Measuring and Incorporating Family Spillover Cost and Health Consequences in Economic Evaluation of Child Health Interventions

by

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Abstract

Background: A child's health conditions affect family members' health, well-being, and economic well-being. However, these spillover effects are ignored in conventional economic evaluations, resulting in an incomplete understanding of the cost and consequences of child health interventions. Frameworks for including family spillover effects have been proposed but are not specific to pediatric economic evaluations.

Objective: The primary aim was to develop a theoretical framework for incorporating family spillover effects in pediatric economic evaluation. Specific objectives were to (1) summarize methods used in pediatric cost-utility analyses (CUAs) to include family health spillover effects and maternal-perinatal CUAs to integrate health outcomes of pregnant women and children, (2) integrate evidence from theories, theoretical frameworks and models into a theoretical framework, and (3) measure health-related quality of life (HRQoL), care-related quality of life (QoL), mental health service use and time losses from paid labour and/or usual activities for parents of children with a neuroinflammatory disorder(s) (ND).

Methods: A systematic review of the literature was conducted to determine methods used to incorporate health outcomes of family members in pediatric and maternal-perinatal CUAs. A critical interpretive synthesis was performed to develop a theoretical framework for incorporating family spillover effects in pediatric economic evaluation. Empiric data were collected prospectively from the Hospital for Sick Children in a cross-sectional study. Descriptive statistics were used to describe time lost from paid labour and/or usual activities, HRQoL, carer-related QoL and mental health services.

Results: Considerable heterogeneity was observed in methods applied to incorporate health outcomes of family members in pediatric and maternal-perinatal CUAs. In the proposed theoretical framework 'conducting economic evaluation from a pediatric family perspective,' the family is a unit of analysis, where family costs and consequences related to a child's illness or disabilities are derived from all family members and incorporated in the analysis. Findings from the cross-sectional study indicated reduced HRQoL and carer-related QoL, and time lost from paid labour and/or usual activities of parents of children with ND.

Conclusion: The thesis presents a theoretical framework 'conducting economic evaluation from a family perspective' for incorporating family spillover effects in pediatric CUAs. This can be used to develop empirical methods to include family spillover effects in pediatric CUAs.

Key words: spillover effects, cost-utility analysis, pediatric neuroinflammatory disorder(s), theoretical framework.

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Dedication

This thesis is dedicated to my family, Bimala Bhandari, Bimarsh Lamsal and Brihat Lamsal.

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Abbreviations

ASD-Autism spectrum disorder

ADHD- Attention Deficit Hyperactivity Disorder

CADTH-Canadian Agency for Drugs and Technologies in Health

CarerQol- Care-related quality of life instrument

CEA-Cost-effectiveness analysis

CUA-Cost-utility analysis

DALY-Disability-adjusted life years

ICER-Incremental cost-effectiveness ratio

ICD- International Classification of Diseases

HRQoL-Health related quality of life

HST-Highly specialized technologies

HUI-Health Utilities Index

HUI2- Health Utilities Index Mark 2

HUI3- Health Utilities Index Mark 3

LMICs- Low-and middle-income countries

QALYs-Quality-adjusted life years

QHES- Quality of Health Economic Studies

QoL-Quality of life

NDD-Neurodevelopmental disorders

ND-Neuroinflammatory disorders

NLSCY-National Longitudinal Survey of Children and Youth

NICE-National Institute for Health and Care Excellence

PBAC-Pharmaceutical Benefits Advisory Committee

TA- Technology Appraisals

TOLAC-Trial of labor after one previous caesarean delivery

1 Introduction

The overarching aim of Chapter one is to increase the understanding of how having a child with a chronic illness or disability affects the welfare of his or her family members and the importance of including health, well-being, and economic impacts in economic evaluation to measure the full effects of a child's health or treatment. This chapter first provides an overview of the aim of economic evaluation and its use in many jurisdictions around the world. It then provides definitions of family and caregiving effects and family health and cost spillover effects in the context of pediatric health. A new conceptual framework for family spillover effects due to a child's illness or disability is presented at the end of the chapter. Chapter one concludes with the study rationale and objectives.

1.1 Background

Economic evaluations have their roots in welfarist and/or extra-welfarist approaches, of which the primary goal is to inform decision-makers on the cost-effectiveness of comparative healthcare interventions to maximize net benefits from available and constrained resources (Basu & Metlzer, 2005; Brouwer, Culyer, van Exel, & Rutten, 2008; Coast, Smith, & Lorgelly, 2008; Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015; D. Meltzer, 2001). Economic evaluation in healthcare compares the cost and consequences of two or more healthcare interventions. The term 'consequences' is also referred to as 'outcomes,' 'benefits,' or 'effects' in economic evaluation literature. The economic evaluation provides information to healthcare decision-makers on the efficient use of limited resources to maximize health benefits. Under the welfarist approach, societal welfare is the function of individual welfare (known as individual utility)(Brouwer et al., 2008; Coast et al., 2008). Utility relates to individual satisfaction derived from consuming a given good or/and services. The goal of any resource allocation scheme is to maximize societal welfare. The welfarist approach is based on the Potential Pareto Improvement that individuals are themselves the best judges of what contributes most to their utility and how much that contribution is, and if one person can be better off (increase in utility) without another being worse off (decrease in utility), there is an improvement in societal welfare (Brouwer et al.,

2008; Coast et al., 2008). The affected group of individuals are the primary source of valuation. Furthermore, the welfarist approach is based on 'consequentialism,' which implies that utility can only be derived from the outcomes of behaviour and processes rather than the processes themselves or intentions that led to the outcomes (Brouwer et al., 2008). Within a welfarist world, health services are considered as goods and services that can be produced, and the consumption of these health services then results in utility, as for the other good and services. Cost-benefit analysis (CBA), where the health outcomes are valued in monetary terms using willingness-to-pay (WTP) methods, directly reflects the theoretical basis of the welfarist approach (J. Buchanan & Wordsworth, 2015; Coast et al., 2008) but the principles are espoused in CEA and CUA as well.

While the welfarism approach exclusively focuses on individual utilities and benefit (or QALY) maximization, extra-welfarism broadens the evaluation space to include other measures and indicators of well-being, such as health gain, caregiver burden, and capabilities and is focused on the *distribution of benefits* to promote equity (Brouwer et al., 2008; Coast et al., 2008). The aim of the welfarist is generally to maximize health benefits from a fixed health care budget. The extra-welfarist approach differs from the welfarist perspective in four critical aspects: i) it permits the use of outcomes other than utility; ii) it permits the use of sources of valuation other than the affected individuals; iii) it permits the weighting of outcomes according to principles that do not need to be preference-based, such as which segments of the population benefits; iv) it permits interpersonal comparisons of well-being in a variety of dimensions, thus enabling movement beyond Paretian principle (Brouwer et al., 2008).

In publicly funded healthcare systems, economic evaluations are increasingly used in the decision-making process, funding, reimbursement, and pricing of a new pharmaceutical product. For example, in Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH), responsible for providing information on the efficiency of drugs and medical devices to provincial health care decision-making entities, requires the comparative analysis of new and existing interventions regarding cost and health outcomes (Canadian Agency for Drugs and Technology in Health (CADTH), 2017). In recent years, the most common types of economic

evaluation in healthcare have been cost-effectiveness analysis (CEA) and, a particular type of CEA, cost-utility analysis (CUA), In recent years, the most common types of economic evaluation in healthcare have been cost-effectiveness analysis (CEA) and, a particular type of CEA, cost-utility analysis (CUA), of which the theoretical foundation is rooted in the extra-welfarist approach (J. Buchanan & Wordsworth, 2015; Coast et al., 2008; Kwon et al., 2019; Neumann et al., 2018; S. Sullivan, Tsiplova, & Ungar, 2016). Both types of analyses evaluate the cost and consequences of at least two alternative interventions, and usually, the result is presented as the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per additional unit of health outcome produced by one intervention compared to an alternative intervention. While both types of analyses are increasingly being used in the decision-making process, a CUA is preferred because health benefits are expressed in QALYs. The QALY includes the effects of an intervention on both the length and quality of life (QoL) and provides a standardized framework for making a comparison of the value of interventions across clinical areas and patient populations (Drummond et al., 2015). The CUA is the recommended type of economic evaluation in guidelines across the world, including in Canada, the UK, and Australia (Australian Government, 2016; Canadian Agency for Drugs and Technology in Health (CADTH), 2017; National Institute of Health and Sciences (NICE), 2013).

An economic evaluation can take various perspectives. *Perspective* is defined in the economic literature as the point of view from which the economic evaluation is being performed and, therefore, determines the cost and effects to include in the analysis (Drummond et al., 2015). A *public health payer perspective* includes healthcare costs borne by the publicly subsidized health system program, such as a provincial government program, and health effects are limited to patients. A *societal perspective*, in theory, is broader and includes all costs and effects regardless of where, when or on whom they fall on, including productivity losses of individuals (patients) and their family members and effects on the health and well-being of family members or others (Brouwer & Koopmanschap, 2000; Drummond et al., 2015). A healthcare perspective disregards the full societal value of the intervention. Hence, decision-makers are presented with partial assessments of interventions, which may lead to suboptimal decisions.

Many jurisdictions around the world take a *public healthcare payer perspective* when making healthcare allocation decisions on how to expend their healthcare budgets ignoring the potential effects (positive and negative) of their illness on family members. Likewise, economic evaluations of a child health intervention, for example, focus on the child when collecting costs and outcomes. However, it would be uncommon to identify a scenario where a child's health condition does not have significant effects on the quality of life and/or well-being of family members and vice-versa (Baldwin, 1990; Dey, Castro, Haug, & Schaub, 2019; Khanna et al., 2011; Lach et al., 2009; Sharpe & Rossiter, 2002). Details related to how a child's illness or disability affects family members' health, well-being, and economic well-being are described in Section 1.2.3.

Failure to include these complex and sometimes opposing effects on family members in economic evaluations results in an incomplete understanding of the cost and consequences of a child's health intervention. It can bias the cost-effectiveness evidence used to inform decision-making. Moreover, excluding the effects of improvements or decline in family members' health and well-being due to a child's health intervention or treatment is inconsistent with the goal of welfare economics, which is to maximize health gain across all the population from available healthcare resources. Furthermore, it poses a risk for the implementation of interventions that reduce population health. Only by measuring relative health and cost spillover effects on family members, and their inclusion in a CEA can a societal decision-maker such as the government, who makes health care funding and policy decisions to maximize the health of the population they serve, understand the full impacts of child health interventions.

Guidelines on CEA across the world increasingly consider the inclusion of selected spillover effects for people other than the patient in the reference case or non-reference case analysis in the CEA conducted from a societal perspective (Canadian Agency for Drugs and Technology in Health (CADTH), 2017; National Institute of Health and Sciences (NICE), 2013; Neumann, Sanders, B., Siegel, & Ganiats, 2017) but do not offer practical guidance on methods for inclusion of health and cost spillover effects in economic assessments. Also, none of these guidelines are explicit about the inclusion of health spillover effects. For instance, the Guidelines

for the Economic Evaluation of Health Technologies in Canada (CADTH guidelines) recommend reporting a reference case from a publicly funded health care payer perspective, which only includes cost and outcomes that are relevant to the Canadian public payer perspective (provincial/territorial government) (Canadian Agency for Drugs and Technology in Health (CADTH), 2017). The CADTH guidelines recommend that any spillover impacts should be addressed in the non-reference case analysis, broader government payer, or societal perspectives. The CADTH guidelines emphasize only cost spillover effects (i.e., lost time due to informal care) and do not state how to include them in economic evaluations. Notably, the National Institute for Health and Care Excellence (NICE) in the UK explicitly says, *"For the reference case, all direct health effects, whether for patients or, when relevant, other people (principally carers) should include in the analysis*" (National Institute of Health and Sciences (NICE), 2013). This could be due to the lack of theoretical and empirical established methods to include impacts on family members in the CEAs.

1.2 Family Spillover Effects of Pediatric Illness on Family Members

This section defines the family effects, caregiving effects, and different types of family spillover effects in the context of pediatric health. It then reviews the prior proposed conceptual framework in estimating the costs for children with disability and Perry's stress model in families of children with disability (Anderson, Dumont, Jacobs, & Azzaria, 2007a; Perry, 2004). Finally, a new conceptual framework for family spillover effects due to a child's health is proposed and discussed in greater detail.

1.2.1 Description of Family Effects and Caregiving Effects

Family effects can be defined as the positive or negative impacts of a child's health on family members' health and/or well-being and/or economic well-being (Bobinac, van Excel, Rutten, & Brouwer, 2010, 2011). Such effects include a burden on physical, mental, and social health and productivity. These effects occur in caregiving and non-caregiving family members due to physical presence, emotional connectedness, and altruistic preference for the child health-family members' concerns about their child's health and well-being even if they are not affected by the

disease or disability (Becker, 1981; Bobinac, van Excel, et al., 2010; Brouwer, 2006). Furthermore, caregiving effects can be categorized into 'formal caregiving' and 'informal caregiving.' *Informal caregiving* in the family context with a child with an illness or disability can be defined as unpaid support and assistance provided by a single or multiple family members to an affected child (Bobinac, van Excel, et al., 2010; Brouwer, 2006). Some full-time informal caregivers may receive financial support from the federal and provincial governments in the form of tax credits (Simpson & Stevens, 2016). An *informal caregiver* is a family member (typically a father, a mother, or both) for a child with an illness or disability. Informal care tasks may include helping a child in day-to-day activities such as bathing, feeding and mobility, taking a child for frequent medical checkups and treatments. In some situations, informal caregivers may provide complex care such as managing medications, preparing special diets, and operating medical equipment and devices (B. C. Dias et al., 2019; Elias & Murphy, 2012). In contrast, *formal caregiving* is defined as remunerated support or assistance provided by professional caregivers (Bobinac, van Excel, et al., 2011). These individuals are trained and have education in providing care and are typically outside the family.

1.2.2 Description of Spillover Effects

Family and caregiving effects are commonly known as 'spillover effects,' 'spillovers,' and 'externalities' within the health economic literature and can be categorized into 'cost spillover effects' and 'health spillover effects' (Basu & Metlzer, 2005; Labelle & Hurley, 1992; Muir & Keim-Malpass, 2020). In the First Panel of Cost-Effectiveness in Health and Medicine, the spillover effects are identified in terms of externalities "as a positive or negative market exchange impacting individuals or groups who are not direct participants in such exchange (page 66) (Russell, Gold, Siegel, Daniels, & Weinstein, 1996)." In a case of a two-person household consisting of a patient with prostate cancer and his/her spouse, Basu and Meltzer defined spillover effects as the spouse's health effects and productivity losses resulting from the patient's health status (Basu & Metlzer, 2005). Based on the welfarist approach, the authors described health effects as the sum of indirect effects on a patient's utility through a family member's utility and direct effects on a family member's utility. In contrast, Al- Janabi and colleagues refer to spillover effects as impacting broader welfare on family members, not just utility, which extends

the individual utility of the welfarist approach with 'nonutility' things relevant to the individual, such as health (Al-Janabi, Van Exel, Brouwer, & Coast, 2016)

Research in other disciplines, such as sociology, has discussed *spillover* as unintentional impacts of policy, process or phenomenon on societal institutions and outcomes. A sociological approach puts a broader lens to the network of spillover effects from family networks to population, institution, communities, or geographic areas (Muir & Keim-Malpass, 2020; Rønningsdalen Kunst et al., 2014; Timmermans, Orrico, & Smith, 2014). Some sociology literature on stress has referred to *spillover* as the direct transfer of mood, affect or behaviour from one setting to another (Repetti, 1987). Finally, psychological literature on marital relations and parent-child relations has defined *spillover* as positive or negative impacts on the parent-child relationship due to marriage quality, which in turn shapes child behaviour. For example, parents who are in a troubled marriage can prevent their children from observing their marital conflicts. However, they cannot prevent them from the negative impact marital discord has on the parent-child relationship, leading to child behaviour problems (Erel & Burman, 1995).

1.2.2.1 Description of Family Spillover Effects

As mentioned earlier, this chapter aims to describe spillover effects on all family members of a child with a disability or illness; hence, we will refer to the spillover effects as '*family spillover effects'* from here onward. Analyses of family spillover effects may be confounded by parallel but unrelated health changes in family members, such as changes in family members' health due to their own health conditions. Thus, it is necessary to understand the relationship between the child's health and health and well-being (including economic well-being) of the family members while defining family spillover effects. For instance, *family spillover effects* for parents are the extent to which the parents' health and/or healthcare costs are attributed to the child's health, when all else is kept constant. In the context of the counterfactual framework, the family spillover effects are defined as the difference in parents' health, and well-being (and/or parents' costs such as the cost from productivity loss out of pocket expenses) and the health and well-being of the parents (and/or parents' cost such as the cost from productivity loss, out of pocket expenses) would have experienced had the child had been in perfect health when all other factors

are held constant (Höfler, 2005; Krieger & Davey Smith, 2016). In the context of pediatric economic evaluation, family spillover effects can be defined as the positive or negative health effects and costs that extend beyond a health intervention's recipient- a child with a disability or illness- to family members.

1.2.2.1.1 Family Cost Spillover Effects

Family cost spillover effects refer to the impact of illness or disability of a child on the economic well-being of family members or the family as a whole. Family members can experience family cost spillover effects for various reasons such as financial losses (productivity cost) due to having to reduce working hours or quit employment to care for a child with an illness or disability, out-of-pocket expenses for treatments for a child's health, and the costs of family members' health service use for problems caused by anxiety and stress stemming from providing caregiving (Anderson et al., 2007a; Davis, Shelly, Waters, Boyd, Cook, & Davern, 2010; Lovell, Moss, & Wetherell, 2012; Perry, 2004; Stabile & Allin, 2012).

1.2.2.1.2 Family Health Spillover Effects

Family health spillover effects refer to the impact of a child's illness or disability on the health family members (because they 'care of a child' or are informal caregivers). There are at least four mechanisms by which a child's health condition can generate family health spillover effects — first, witnessing the suffering or worse health state of a loved one- a child (Becker, 1981; Bobinac, van Excel, et al., 2011; Brouwer, 2006). Second, threats to their freedom, professional career, personal relationships, and reduced feelings of self-efficacy (Alaee, Shahboulaghi, Khankeh, & Kermanshahi, 2015; Dieleman, Van Vlaenderen, Prinzie, & De Pauw, 2019). Third, changing behaviours due to a child's health or illness (for instance, parents may engage in unhealthy behaviour such as smoking or drinking to cope with stress and anxiety stemming from a child's disability or illness) (Burton, Lethbridge, & Phipps, 2008b; M. H. Lee, Park, Matthews, & Hsieh, 2017). Finally, fourth, providing informal care (i.e., performing physically and emotionally demanding caregiving for prolong period results in psychological distress, depression, anxiety, and other mental health problems in informal caregivers) (Cohn et al., 2020; Dey et al., 2019; M. Pinquart, 2018; Martin Pinquart & Sörensen, 2003).

In addition, effects on the well-being of family members may also occur- *Family well-being spillover effects*. Definition of well-being varies widely; at its broadest, the concept encompasses all the domains of quality of life such as health, social relationships, and levels of independence (Bobinac, van Excel, et al., 2011). Well-being effects refer to the impacts of a child's illness or disability on the general quality of life. i.e., happiness, life satisfaction. For instance, having to perform unpleasant activities and the need to give up leisure time might reduce well-being while not affecting the health of family members (Brouwer, 2006; Brouwer, Exel, & Tilford, 2010).

1.2.3 A Conceptual Framework for Family Spillover Effects

Many existing models have conceptualized family spillover effects in the context of only one domain of health and well-being, such as psychological impacts or social impacts or economic burden on parents (Anderson et al., 2007a; Davis, Shelly, Waters, Boyd, Cook, & Davern, 2010; Kutty, 2008; Perry, 2004; Popova, Stade, Lange, & Rehm, 2012; P. Raina et al., 2004; Stabile & Allin, 2012; Tsimicalis, Stevens, Ungar, McKeever, & Greenberg, 2011). For instance, Anderson's model for measuring the economic burden incurred by families who care for children with disabilities considers the family as the unit of analysis (Anderson et al., 2007a). The model illustrates that family time (caregiving time, employment time, leisure time, and sleep time), family income, and goods and services consumed along with disability characteristics such as severity, functional limitations, and aptitudes constitute a framework for understanding the economic burden related to the child’s disability. The model further demonstrates that because of a dynamic relationship and collective decision-making within families, changes in the health of one family member or a decision to invest in a child's health over another family member can affect other family members' health and resource consumption. Perry's stress model in families of children with developmental disabilities (DD) describes positive and negative effects on parents as the results of stressors intersecting with personal (e.g., coping strategies, beliefs), family (family functioning, marital satisfaction, socioeconomic status of the family), formal (professional or paraprofessional intervention) and social resources (e.g., family, friends, social organizations) available to deal with stressors (Perry, 2004). Stressors are defined as subjective and objective child characteristics such as: level of dependency in self-help tasks, cognitive or developmental level, frequency and severity of maladaptive behaviour, and type of DD, and

family characteristics related to parents' employment, illness of other family members and family's financial problems. The authors further highlight that stress does not occur due to a single event, nor is it a unitary phenomenon. It is, instead, a mix of circumstances, experiences, responses, and available resources. A comprehensive conceptual framework that describes family spillover effects in the context of pediatric economic evaluation is discussed below.

Prior to discussing mechanisms by which family cost, health, and well-being spillover effects happen in families of a child with a disability or chronic illness in greater detail, it is crucial to understand the uniqueness of child health in terms of development, dependency on family members and patterns of resource uses. These impact the measurement, assessment and valuation of health outcomes and costs of pediatric intervention, including family spillover effects. A child's development and subsequent transformation into adulthood occur from the interplay of several factors at the individual, family, society, and environment levels (Bronfenbrenner, 1986; Jack, 2000; Piaget & Cook, 1952; Ungar, 2011; Ungar & Gerber, 2010; Lev Semenovich Vygotsky, 1980). This transformation is characterized by sequences of physical, emotional, behavioural, cognitive, and social changes. Children are not a homogenous subpopulation; instead, they have different stages of development, such as fetus, neonates, infant, toddler, pre-school age, school-age, and adolescent (Ungar & Gerber, 2010). Therefore, the same methods of measuring, assessing and valuing health outcomes and costs and family spillover effects do not apply across the developmental stages. For instance, very young (e.g., infant, toddler, and pre-school age) and/or developmentally disabled children may lack cognitive and communication skills, limiting their ability to comprehend and complete self-administered health questionnaires. And there is a paucity of child-specific outcome measures. Proxy reporters such as parents are used to elicit health values and utilities (Pickard & Knight, 2005; Thorrington & Eames, 2015). Parents or caregivers can be useful proxy respondents as they are the people most familiar with their child's health, but such valuations can be influenced by anxieties stemming from the caregiving burden and competing priorities represented by other children in the family. This may lead to double counting of 'family health spillover effects, on parents or caregivers. Furthermore, a dynamic, complex, and changing dependency relationship exists between the child's development and the family. This relationship is bi-directional, in which a child and family

members mutually influence each other's well-being and differs at various stages of development (Bakula et al., 2019; R. Q. Bell, 1968; J. Lee, 2013; Pardini, 2008; Scherer, Verhey, & Kuper, 2019). For example, the influence of the parent-child relationship on the adolescent is different from the infant due to the behavioural and emotional changes or because adolescents gain more autonomy and interdependence (A. J. Sameroff & Chandler, 1975). Therefore, the impacts on parents' health and well-being when the child is an infant could differ from when they grow up to adolescence.

Second, children depend on their parents (adults) for healthcare needs. Given the complex and changing relationships between a child's health and well-being and family members' health and well-being, investing in one child's health affects the health resources used by other family members, such as unaffected children and parents (Anderson, Dumont, Jacobs, & Azzaria, 2007b; Apps & Rees, 2001; Burbach & Peterson, 1986). Measuring the family cost spillover effects using a household or collective approach could the best approach to measure the family spillover costs. Finally, the need for healthcare services also differs between age groups. For instance, health care needs for newborns and infants are perinatal screening and immunization and for young children are the treatment for acute illness and injuries, preventive care, and immunization (Lindsey, Kampmann, & Jones, 2013; Spittle et al., 2010). When a disease or disability is present in young children, healthcare providers often rely on parents (and/or children) for symptom assessment (symptoms, functional capabilities, emotional and social changes) because very young children have difficulties verbalizing symptoms. Parents' subjective experience with the child's disease impacts the system appraisal, and ineffective system appraisal can result in decreased job productivity and family stress (Annett, 2001). Understanding the uniqueness of child health, child development, interdependency, and patterns of resource use, and how these impact family members' health and well-being and economic well-being is essential to conducting pediatric economic evaluation and incorporating family spillover effects in pediatric economic evaluation.

The existing adult-based theoretical frameworks for incorporating family spillover effects do not recognize the difference between the child's health and well-being and an adult's health-being,

which impacts the measurement, valuation, and incorporation of the family spillover effects (Basu & Meltzer, 2005; Al-Janabi et al., 2016). Both frameworks do not discuss or consider the different stages of child development and their impact on family members. For instance, the spillover effects on family members when an infant is ill differ from when an adolescent is ill. This needs to be considered while incorporating family spillover effects because it impacts the measurement, valuation and integration of spillover effects. Furthermore, Basu and Meltzer's framework assumes that an individual makes decisions about purchasing medical care based on maximizing his or her own utility. However, this assumption does not hold in pediatric economic evaluation, where parents or caregivers are often the decision-makers for children's healthcare needs (Basu & Meltzer, 2005). Therefore, there is a need for a pediatric-specific theoretical framework that considers the uniqueness of a child's health in terms of development, dependency on family members and patterns of resource uses.

Moreover, some children are born with severe diseases or disabilities. These congenital anomalies can vary from mild to severe and can be caused by gene defects, environmental teratogens, and micronutrient deficiencies (Dolk & Vrijheid, 2003; Li et al., 2021). A child with a congenital disorder may experience a disability or health problems throughout life and may significantly impact families (Costa, Williams, Martindale, Stock, & Team, 2019; Fernández-Alcántara et al., 2015; Lumsden, Smith, & Wittkowski, 2019). Moreover, it is important to understand that a family is a collective unit in which all family members affect each other's health and well-being (Bortz, Berrigan, VanBergen, & Gavazzi, 2019; Bowen, 1966). Often, decisions to consume health care services and goods are made collectively to maximize the health and well-being of all the family members (Anderson et al., 2007a; Apps & Rees, 2001; L. Jacobson, 2000). The impacts of these complex and changing relationships are even more significant for families with a child with a chronic illness or disability. Children with chronic illness or disability often have functional limitations throughout their lifespan (Amato et al., 2014; Kennes et al., 2002; Mâsse, Miller, Shen, Schiariti, & Roxborough, 2013; Morales, Siatkowski, & Warman, 2000). These children depend on their family members to seek and obtain appropriate treatments, impacting their development and well-being.

This section is organized as follows. First, how do family spillover effects occur in parents, siblings, and other family members (grandparents) is described based on the literature review. Second, how family factors (parents' income, employment status, education, and occupation), community-level factors (peers, school, daycare, and neighbourhood), cultural context (cultural and religious beliefs of the family), external events (such as pandemic COVID-19, H1N1 pandemic, economic recession), and national and provincial health policies, and access to health and social care services impacts family spillover effects is described. Finally, a conceptual framework on how the family spillover effects occur in a family with a child with chronic illness or disability is presented.

1.2.3.1 Impacts of a Child's Illness or Disability on Parents

In a family with a child with a chronic condition or disability, parents hold a primary role in caring for and supporting a child with an illness or disability. Children with a severe chronic illness or disability require lifetime comprehensive caregiving for day-to-day activities such as feeding, bathing, dressing, and transport to recreational activities, to being brought to frequent medical checkups or treatments (Aronson, Cleghorn, & Goldenberg, 1996; Pakenham, 2007). Parents of children with illness or disability experience family spillover effects through caregiving and family effects. Studies have identified parents' struggles, including financial difficulties related to reduced income and increased expenditure, loss of leisure and sleep time, physical and mental health, a threat to their professional career and negative impacts on the marital relationship (Alaee et al., 2015; Dieleman et al., 2019; Lamsal & Zwicker, 2017; Petersen et al., 2020; Plumb et al., 2015; Stabile & Allin, 2012).

This section is organized as follows. First, family costs that occur in parents of children with chronic illness or disability will be discussed. Second, the ways in which family health spillover effects occur in the parent with chronic illness or disabilities will be presented. Finally, the ways that the magnitude of health spillover effects on parents can vary according to time since diagnosis and the types and severity of children's illness or disability and age will be discussed.

To provide care for a child with a disability or chronic illness, parents may need to give up work, reduce working hours (or increase working hours to increase income) or change jobs to provide

informal care resulting in productivity losses. Furthermore, they may need to call late into work or take frequent sick leave (paid or unpaid) due to the unpredictable course of treatment and prognosis of disease or disability and their own ill health caused by physical and mental strains of caregiving. The estimates of parents' employment loss due to caring for a child with a disability or a chronic illness vary widely in the literature. Studies have estimated that child disability reduces maternal employment by 3 to 15 percentage points, and among the employed, reduces work hours up to fifteen hours per month (Stabile & Allin, 2012). A report by Human Resources and Skills Development Canada reports that in 2006 parents of children (age 0 to 14 years) with severe disabilities were twice as likely to leave a job because of their children's conditions than parents of children with mild or moderate disabilities (26.8% versus 10.2%) (Human Resources and Skills Development Canada, 2011). With few exceptions, most studies studying the impacts of children's disabilities on parents' employment do not include effects on fathers' employment. Some fathers of young adults with multiple disabilities reported working fewer hours than usual, while others worked long hours to meet the financial needs of the family (Einam & Cuskelly, 2002).

Leisure time losses of parents of children with chronic illness or disability have not been studied as extensively as losses in employment. A few existing studies showed that parents with chronically ill or disabled children did not have enough time for personal care, socializing and leisure activities (Brandon, 2007; Janneke Hatzmann, Niels Peek, Hugo Heymans, Heleen Maurice-Stam, & Martha Grootenhuis, 2014; McAuliffe et al., 2022; McCann, Bull, & Winzenberg, 2012; Taanila, Järvelin, & Kokkonen, 1999). Mothers raising children with disabilities had four hours less spent per workweek on personal care than those raising children without disabilities (Brandon, 2007). The relationship between disrupted sleep patterns (frequent night waking, early morning wake time, and shorter total sleep time) in parents of children with chronic illness or disabilities has also received limited attention (L. J. Meltzer & Moore, 2008; L. J. Meltzer, Sanchez-Ortuno, Edinger, & Avis, 2015; Micsinszki, Ballantyne, Cleverley, Green, & Stremler, 2018). Parents of children with epilepsy, cerebral palsy, autism spectrum disorder (ASD) and diabetes reported changing sleeping arrangements, poorer sleep quality and sleep deprivation due to frequent night waking to check on their children and stress related to

caregiving (R. Y. Hulst et al., 2021; L. J. Meltzer, 2008; L. J. Meltzer & Mindell, 2006; Micsinszki et al., 2018; Wayte, McCaughey, Holley, Annaz, & Hill, 2012). In a study, parents of children with severe atopic eczema reported they spent 40 to 45 minutes per night attending to their child-health-related needs (Moore, David, Murray, Child, & Arkwright, 2006).

Furthermore, parents of children with chronic illness or disabilities may incur out-of-pocket expenditures, such as payments for coinsurance and deductibles for the hospital and office-based visits, prescription medications, buying special equipment for children, and travel costs related to obtaining services for the child's health or their own health due to providing care for their child (Cakir, Frye, & Walker, 2020; Lukemeyer, Meyers, & Smeeding, 2000; Stabile & Allin, 2012). Some estimates show that parents of children with disabilities spend upwards of $500 per year on out-of-pocket medical expenses (Stabile & Allin, 2012). Mumford and colleagues estimated the non-medical out-of-pocket cost for families of hospitalized children in Australia (Mumford et al., 2018). On average, parents spent 89 Australian dollars (AUD) per day on travel and AUD 36 on meals and accommodation while their children were hospitalized.

Co-occurring with the effects on parental employment, leisure time, disruptive sleep, and out-of-pocket costs, a child’s illness, or disability impacts parents’ physical and mental health. Family health spillover effects can occur in parents through family effects, e.g., by witnessing the worsening health of a beloved child, threats to parents’ personal freedom, and disruptions to their professional career and personal relationships. Also, as well as reduced feelings of self-efficacy, changing behaviours due to a child’s health or illness and providing informal care. These health effects can occur for a variety of reasons. First, parents will have concerns about a child's future and treatments for altruistic reasons. For instance, children with chronic conditions such as neurodevelopmental disorders (NDD) or neuroinflammatory disorders (ND) may have limited cognitive, linguistic, communication, and social skills. These deficits continue throughout their life spans (Amato et al., 2014; Schalock et al., 2010; Tardieu, Banwell, Wolinsky, Pohl, & Krupp, 2016). Consequently, parents continuously worry about their children's future, such as thinking about how children will cope with the transition from childhood to adulthood and what sort of future, they will have (C. A. Martin, N. Papadopoulos, T. Chellew, N. J. Rinehart, & E.

Sciberras, 2019; Zebrack, Chesler, Orbuch, & Parry, 2002). Studies showed that parents of children with developmental disabilities do not get proper sleep and have frequent awakenings at night worrying about their child's health (R. Y. Hulst et al., 2021; L. J. Meltzer, 2008; L. J. Meltzer & Mindell, 2006; Wayte et al., 2012).

This prolonged worrying often has significant impacts on parents' mental health (Fairfax et al., 2019; Lloyd & Hastings, 2009; Ogston, Mackintosh, & Myers, 2011). Studies consistently report higher levels of psychological health problems, including higher levels of perceived stress, depression, and lower levels of subjective well-being among caregivers of children with disabilities (Brehaut et al., 2004; Lovell et al., 2012; M. Pinquart, 2018). For example, a population-based Canadian study found that parents (caregivers) of children with health problems had more than twice the odds of reporting symptoms of depression, physical limitations, and chronic health problems compared to caregivers of healthy children (Jamie C Brehaut et al., 2009). Brehaut et al. examined the health of caregivers of children with chronic health problems using the National Longitudinal Survey of Children and Youth (NLSCY) data from 1994–1995 to 2004–2005. The results showed that the poorer self-reported caregiver health was associated with the complexity of child health problems for the entirety of the ten years (Brehaut et al., 2011). Also, having a child with chronic illness or disability and seeing a child go through changes, pain, confusion, and struggles could adversely affect parents' physical, social, and emotional functioning. Some chronic illnesses and disabilities, such as congenital heart defects, infantile cerebral palsy, down syndrome, and spina bifida, develop prenatally and can be identified before or at birth (Dolk & Vrijheid, 2003; Li et al., 2021). For the parents and family members, the discovery that their child has a congenital disease can be shocking and distressing, impacting the health and well-being of the family members (Alkan, Sertcelik, Yalın Sapmaz, Eser, & Coskun, 2017; Costa et al., 2019; Li et al., 2021; Werner, Latal, Valsangiacomo Buechel, Beck, & Landolt, 2014). The birth of a child with disabilities or chronic illness has been associated with feelings related to loss of grief, depression, anxiety, and post-traumatic stress (Fernández-Alcántara et al., 2015; George, Vickers, Wilkes, & Barton, 2007; Poehlmann, Clements, Abbeduto, & Farsad, 2005; Sen & Yurtsever, 2007). Some parents reacted with denial

and refusal to accept when they first learn about their child's diagnosis (Fernández-Alcántara et al., 2015; Huang, Kellett, & St John, 2010).

Furthermore, family health spillover effects can also occur through guilty feelings. Parents may feel guilty or experience self-blame for not being able to provide what they perceive as a sufficient amount of care for a child despite their full commitment to them and not spending a sufficient amount of time with their other healthy children, if applicable (Findler, Jacoby, & Gabis, 2016; Golla, Mammeas, Galushko, Pfaff, & Voltz, 2015). Secondly, parents experience stress and anxiety due to threats to their freedom, professional career, personal relationships, and reduced feelings of self-efficacy even if they do not provide informal care. Third, family health spillover effects might occur due to changing health behaviours of family members due to a child's health or illness. The demands of parenting children with a disability or chronic illness not only impact the health of family members but also may force them to engage in risky health behaviours such as smoking, heavy drinking, and physical inactivity, which in turn impacts the health of the parents. Family caregivers (mothers) of children with disabilities reported higher smoking and physical inactivity rates than family caregivers of children without disabilities (Burton et al., 2008b; M. H. Lee et al., 2017; Schulz et al., 1997).

The magnitude of health effects on parents who take on informal caregiving roles can be higher than parents who do not provide informal caregiving because they must provide care regularly and manage the vast array of problems that confront affected children (Cardinali, Migliorini, & Rania, 2019; Parminder Raina et al., 2004; Sabbeth, 1984; Shah, Ali, Finlay, & Salek, 2021; Ten Hoopen et al., 2020). Parental carer(s) (parent(s) that provide informal care for a child with illness or disability) can experience additional spillover health effects generated through informal caregiving compared to parents who are not informal caregivers. Providing informal care for prolonged periods can induce detrimental effects on parent carer(s)' physical and mental health. These effects are primarily related to caregiving activities — for example, physical strain from lifting and dressing a child or fatigue from hours of informal caregiving. A few studies examining the physical health of parents of children with disabilities reported poorer physical health outcomes than the parent of typically developing children (M. H. Lee et al., 2017; Lovell

et al., 2012). Furthermore, parent carers often need to confront stress and anxieties stemming from the unpredictable course and prognosis of a child's disease or condition. For instance, in children with multiple sclerosis, the relapses occur at unpredictable intervals and are variably severe (Amato et al., 2014). Meta-analyses and systematic reviews concluded that parent carers are at higher risk of anxiety, depression, and other mental health conditions and have lower QoL than parents of unaffected children or the general population (Cohn et al., 2020; M. Pinquart, 2018; Pousada et al., 2013).

Having a loved one, i.e., a child with an illness or disability, can also have adverse effects on the well-being of parents regardless of whether the parent is providing informal care or not. Well-being is a broader concept encompassing all the domains of QoL, including happiness or life satisfaction, which are not captured by health-related quality of life (HRQoL) measures (Brouwer et al., 2010). Informal caregiving may affect caregiver well-being beyond health.

As demonstrated by the evidence above, raising and caring for a child with a chronic illness or disability may have deleterious effects on parents' HRQoL and well-being, consequently increasing their own need for healthcare services. Parents may need to seek support or pay out-of-pocket for healthcare services for their own health problems caused by the higher level of stress or psychological difficulties solely caused by a child's illness or disability. Parents may also experience physical health problems leading to higher medication use and hospitalization. Few studies have examined caregiver health care utilization in general. Informal caregivers of adult patients with bipolar disorder reported using higher mental health services to deal with higher psychological symptoms such as anxiety and depression than less burdened counterparts, even after controlling for sociodemographic and patient clinical variables (Perlick, Hohenstein, Clarkin, Kaczynski, & Rosenheck, 2005). A few other studies showed the association between caregivers' depression and psychological distress with health complaints and the greater use of primary care services and mental health services use than non-caregiver controls (Marrie et al., 2020; O'Reilly, Finnan, Allwright, Smith, & Ben-Shlomo, 1996; Olfson & Klerman, 1992).

Though less commonly noted in the literature, informal caregiving can also positively impact the health and well-being of parents through the feeling of altruism and fulfillment of familial

obligations (Blacher & Baker, 2007; East, 2010). For parents, it can be rewarding to be able to provide care to a loved one. Only a few empirical studies shed light on the positive health and well-being spillover effects on parents; however, numerous qualitative studies have documented the positive effects of caring for a child with a disability or chronic illness with regard to an increased sense of purpose and priorities (Stainton & Besser, 1998), expanded social network (Davis, Shelly, Waters, Boyd, Cook, Davern, et al., 2010), and community involvement increased quality of the relationship with an affected child (Haley et al., 2009; Kearney & Griffin, 2001; Lawton, Moss, Kleban, Glicksman, & Rovine, 1991), and a more positive outlook about the future (Taunt & Hastings, 2002). Moreover, informal caregiving may have positive impacts on the well-being of caregivers through the feeling of performing a meaningful task, i.e., caring for a loved one and being with a child who is ill (Brouwer, van Exel, van den Berg, van den Bos, & Koopmanschap, 2005). When asked, many informal caregivers preferred to provide care to their ill or disabled loved ones themselves rather than handing care over to someone else, such as formal caregivers (Brouwer, van Exel, van den Berg, van den Bos, & Koopmanschap, 2005).

Finally, the magnitude of health spillover effects on parents can vary according to time since diagnosis and the types and severity of children's illness or disability and age. The psychological and emotional toll at the time of initial diagnosis can be tremendous compared to years after the diagnosis. Parents need to adapt to living with a child with illness or disability, including re-defining the parent-child relationship, re-organizing family life, and re-prioritizing individual and family goals (Pousada et al. 2013). Over time, the effects may begin to change with social support, management choices, and coping mechanisms. Multiple studies on pediatric cancer indicate that parents experience higher levels of depression and anxiety close to diagnosis, with their distress declining over time (Kazak, Boeving, Alderfer, Hwang, & Reilly, 2005; Klassen et al., 2007; Pai et al., 2007; Phipps, Long, Hudson, & Rai, 2005; Zheng et al., 2022).

On the other hand, as a child's disability progresses, functional limitations may become more apparent with increasing needs for health care and personal care, resulting in an increased burden on parents. For instance, school-aged children with ASD might struggle to participate in social

activities at school because of deficits in language expression, social relationships, and learning. Therefore, they might need additional support from parents compared to when they are at home. As children with a disability, such as ASD, grow older, it may be harder to manage them when they are upset or aggressive. Parents of school-age children with ASD reported higher stress level than parents of pre-school children with ASD (Goldbeck, 2006).

Interestingly, the magnitude of the family health effects depends on the sex and gender of the parent. Burton and colleagues used the NLSCY to estimate the long-term effects of having a child with a disability on maternal and parental health. After controlling for previous health status and family and sociodemographic characteristics, the authors concluded that mothers experienced a relative decline in health compared to fathers (Burton, Lethbridge, & Phipps, 2008a). The mother's health declined relative to the father's health over the 1994–2000 period in 24.3% of cases; the father's health declined relative to the mother's health in 30.3% of cases in families where there was never a child with a disability or chronic condition.

1.2.3.2 Impacts of a Child's Illness or Disability on Unaffected Siblings

It is estimated that by the ages of four to six, children may spend as much time with a sibling as with a parent (Bank and Kahnm, 2002). It is reasonable to assume that siblings have a significant influence on one another's health and well-being. This relationship becomes indispensable for children with chronic illness or disability as they might need to rely on their unaffected siblings for mobility, personal care, and social supports (Ferrari, 1984; Schamong, Liebermann-Jordanidis, Brockmeier, Sticker, & Kalbe, 2021; Sharpe & Rossiter, 2002). The unaffected siblings of children with chronic illness or disability experience spillover effects primarily through family effects because, in most cases, siblings are not old enough to provide informal caregiving. In some cases, unaffected (adolescents) siblings of children may take on informal caregiving roles due to the high needs of an affected sibling or even provide informal caregiving for other siblings while the parents are focused on the ill child (Dyson, 2010; Floyd, Purcell, Richardson, & Kupersmidt, 2009; Wennick, Lundqvist, & Hallström, 2009). Typically, siblings ≥18 years are away from home at university or college for further education or workforce. Older siblings may provide informal caregiving.

There are two ways in which a child's illness or disability can generate health and well-being spillover effects on unaffected siblings, namely 1) directly from the child's illness or disability and 2) indirectly from the change in family functioning (Lamsal & Ungar, 2019). Like parents, unaffected siblings may have difficulties adjusting and adapting to living with a child with chronic illness or disability at the time of initial diagnosis. They might not fully understand the changes occurring in his/her affected siblings due to chronic illness or disability. Consequently, the lack of knowledge about their sibling's illness negatively impacts the sibling relationship (Roeyers & Mycke, 1995). Unaffected siblings share a strong emotional bond with affected siblings; thus, they may also experience distress from witnessing a loved one suffering. Studies have shown that unaffected siblings of children with chronic illness are vulnerable to experiencing social withdrawal, aggression, depression, anxiety, and isolation due to embarrassment from teasing from peers, inability to play with their siblings, aggressive and annoying acts by their siblings (Moyson & Roeyers, 2012). These negative experiences impact the physical, emotional, and social domains of health. Secondly, health and well-being spillover effects on unaffected siblings occur indirectly from changes in family dynamics after the diagnosis. As mentioned above, raising, and caring for a child with chronic illness or disability requires much time, effort, and tolerance. Parents must re-allocate resources and time to an affected child who needs high-demand diverse care, and it may reduce their capacity to invest in their unaffected child's health and well-being. In this process, an unaffected sibling may be or feel forgotten, disregarded, or neglected; such changes could have adverse effects on a healthy sibling's overall well-being and functioning. For example, the non-availability of a parent who stays at the hospital all day with the ill child can affect the attachment of unaffected children with parents (J. S. Murray, 2000a, 2000b).

Growing up with a sibling with a chronic condition or disability could also positively impact the health and well-being of an unaffected sibling. Few studies have documented the positive impacts on the health and well-being of growing up with siblings with chronic illness or disability compared to negative impacts. The positive impacts can stem from feeling pride and love in helping their brother or sister with their health problem (J. S. Murray, 2000a, 2000b). Studies show that the presence of a sibling with a chronic illness or disability provides

opportunities for greater maturity, responsibility, adaptability, empathy, and responsibility (Corsano, Musetti, Guidotti, & Capelli, 2017; Green, 2013; Wilkins & Woodgate, 2005). Other studies have suggested siblings' experience of caring for and observing their siblings go through a course of illness may give them an appreciation for life that siblings of healthy children may not comprehend (Martinson, Gilliss, Colaizzo, Freeman, & Bossert, 1990; Sargent et al., 1995).

Moreover, health and well-being spillover effects on healthy siblings can occur in those who take on informal caregiving roles — sibling carers. These effects occur due to performing physically or emotionally demanding care tasks, often over long periods. Nevertheless, it is unlikely that unaffected siblings take on full informal caregiving roles because usually, they are too young to take a high level of responsibility for providing support and assistance to affected siblings. Primarily, in a family with children with chronic illness or disability, parent(s) provides informal caregiving. Unaffected siblings might assist parents in feeding, dressing, helping at school and schoolwork, and helping in the mobility of siblings and babysitting for a specified period. In some cases, older siblings of affected children might take on full caregiving responsibility (Chikhradze, Knecht, & Metzing, 2017; Hilário, 2022; Ireland & Pakenham, 2010; Warren, 2007). Like parents, the cost spillover effects could occur in unaffected siblings through school productivity losses, out-of-pocket expenses, and health service use due to health problems caused by a sibling's illness or disability. Empirical data is needed to support these hypotheses.

Lastly, the magnitude of impacts on a sibling of a child's chronic illness or disability depends on other factors such as types and severity of conditions or disability, time since diagnosis, and sibling age. Time since diagnosis and age are essential factors in modulating the spillover effects on unaffected siblings. For instance, for siblings who have adapted to a child's disability or chronic illness, the impact could be lesser compared to those of siblings of children with newly diagnosed disease (Lamsal & Ungar, 2021; Sharpe & Rossiter, 2002).

1.2.3.3 Impacts of a Child's Illness or Disability on Other Family Members

The impacts of a child's illness or disability can extend beyond the parents and siblings to include other family members living or not living in the same household. It is well recognized that other family members, such as grandparents, can play a vital role in raising grandchildren

(Hank & Buber, 2009; Hayslip Jr & Kaminski, 2005; Laughlin, 2010). However, research to date has predominantly focused on the experience of parents. Much less is known about the roles and experiences of other key members in raising and caring for a child with chronic conditions or disability. This section describes the possible mechanisms of family spillover effects on grandparents because of grandchildren's illness or disability.

It has become a standard practice of child welfare agencies to remove abused and neglected children from the parents' custody and place them into the care of a family member, often a grandparent (Ellis & Simmons, 2014). Grandparents may take responsibility for raising a grandchild when parents (or single parents) are unavailable due to illness, substance use, or incarceration (Goodman, Potts, & Pasztor, 2007; Goodman & Silverstein, 2002; Kelley, Yorker, & Whitley, 1997). In some cases, grandparents may share responsibility for raising and caring for children with or without disability or chronic illness in response to the parents' financial needs or work commitments. A study conducted in 10 European countries reported that 58% of grandmothers and 49% of grandfathers looked after at least one of their grandchildren under age 16 years in the preceding year in the absence of their parents (Hank & Buber, 2009).

Similar to parents and siblings, health and well-being effects can occur in grandparents through informal caregiving and family effects. First, caring for grandchildren reduces the time available for self-care, such as exercising, going to doctors (Roe, Minkler, Saunders, & Thomson, 1996), and the time available for engaging in hobbies and socializing (Pruchno, 1999; Pruchno & McKenney, 2002). Second, health and well-being spillover effects can occur in grandparents through witnessing worse health states of a grandchild. Scherman et al. interviewed 32 grandparents of children with special needs regarding their grandchild's disability and the emotional impact it had on their lives. The grandparents expressed their fears and concerns regarding their grandchild's ability to live independently and worries and significantly impacted grandparents' mental health (Scherman et al., 1995). Conversely, caring for a grandchild with or without disability or chronic illness also brings benefits. In a qualitative study, grandparents were asked about the impact of caregiving, and grandparents stated that caring for a grandchild is positively affirming and rewarding (Pruchno & McKenney, 2002). In some studies, grandparent

carers reported feeling closer to their grandchildren and enjoyed the time spent with them (F. Chen & Liu, 2012; Hastings, 1997; Hillman, Wentzel, & Anderson, 2017; Ku et al., 2013). Along with health and well-being spillover effects, grandparent carers may experience cost spillover effects through productivity losses, out-of-pocket expenses, and costs of health service use for their own health due to problems caused by a grandchild's illness or disability. However, there is a lack of evidence to make a causal link.

1.2.3.4 External Factors that Moderate Family Spillover Effects

The second level of the proposed family spillover effect model shows external factors that influence the cost and health spillover effects experienced by family members. As seen in Figure 1, these factors include the socioeconomic status of the family (household income, employment, education, and occupation), community-level factors (peers, school, daycare, and neighbourhood), including where a child grows up, cultural context (cultural and religious beliefs of the family) and unexpected crises (e.g., COVID-19 pandemic and economic crises).

1.2.3.4.1 Family Socioeconomic Status

A family's socioeconomic status (SES) is an important factor that moderates the cost and health spillover effects of illness on family members. The choice by a family member to provide informal care depends on the perceived benefit of investing time to provide informal care versus the benefit of working, the quality of childcare, and its affordability. A mother or father (a caregiver) from a lower-income household is more likely to give up work, reduce working hours, or change jobs to provide informal caregiving (Parish, Seltzer, Greenberg, & Floyd, 2004; Porterfield, 2002). This might be because the family could not afford specialized childcare or a babysitter. Alternatively, they might need to work extra hours to afford specialized childcare (Bauer & Sousa-Poza, 2015; Do, Cohen, & Brown, 2014; Hughes et al., 2014); consequently, they will have less time to care for the child and self-care, resulting in a poorer parent-child relationship and negative impacts on the parents' health (Adelman, Tmanova, Delgado, Dion, & Lachs, 2014).

The parents from a high-income household may afford high quality and/or specialized childcare (Dowsett, Huston, Imes, & Gennetian, 2008; A. L. Sullivan, Farnsworth, & Susman-Stillman, 2018) and continue to work and develop their professional careers; therefore, they may carry a smaller finanical burden.The amount that parents from higher-income households spend in providing care (buying special equipment, out-of-pocket cost if necessary, or other related and unrelated medical costs) for their child is likely be higher than that of parents from lower household incomes (Meyers, Lukemeyer, & Smeeding, 1998; Newacheck & McManus, 1988; Parish & Cloud, 2006). However, the low-income families are vulnerable to burdensome out-of-pocket costs (Newacheck, Inkelas, & Kim, 2004; Newacheck & Kim, 2005). High-income parents may experience positive effects on well-being (where the parents feel better because they can provide the best care to their child) compared to low-income parents. Similarly, the scope of spillover effects may vary systematically by parents' occupations and education (A. Kish, P. Newcombe, & D. Haslam, 2018; Saunders et al., 2015). The knowledge gap hypothesis suggests that individuals with a higher education level absorb information faster than those with a lower level of education (Viswanath & Finnegan Jr, 1996). Therefore, parents with a higher level of education may acquire and adopt information relevant to parenting a child with chronic illness or disability more rapidly than parents with a lower level of education. At the same time, parents with higher education may experience higher levels of anxiety related to searching for "the best care" and expecting more than available. In summary, the above-discussed evidence shows that financially secure and educated parents may experience impacts differently than parents from lower SES. Further empirical evidence is necessary to support this hypothesis. Therefore, household income and parents' education and occupations significantly affect the magnitude of spillover effects for family members.

1.2.3.4.2 Community (Peers, School, Daycare, and Neighbourhood)

The child's health and well-being are embedded in multiple relationships and contexts outside the home, such as peer groups, the school, daycare, and the neighbourhood (Bronfenbrenner, 1986; A. Sameroff, 2009; Ungar & Gerber, 2010).. The effects of these environmental factors on health and well-being for children, including children with disabilities or chronic illness, are significant. School and daycare are critical places where children learn socialization skills. Typically,

children with disabilities or chronic illnesses require additional resources or have special needs while attending schools because of their deficits in learning, social, and behaviour skills (Winn & Hay, 2009). As a result, parents may need to be in regular contact with the school to ensure all supports are in place The complexity of school dynamics and the need to communicate with teachers and school personnel can be overwhelming for parents of children with disabilities or chronic illnesses. Parents who send their children to schools where there is a lack of infrastructure and support, including lack of trained teachers, lack of classroom support learning resources, and poor coordination, may have higher levels of stress and frustration compared to parents who send their children to schools that have adequate infrastructure for children with disability (Janus, Kopechanski, Cameron, & Hughes, 2008; Limaye, 2016; Minnes, Perry, & Weiss, 2015).

Another important environmental factor that may influence the spillover effects on family members is a child's relationship with peers. Peer effects have been identified as the most significant environmental factors in developmental psychology (Harris, 1998). Evidence has shown that children who have positive relationships with peers can easily adjust in schools and have increased academic success (Hoxby, 2000; Ladd, 1990). Some children with disabilities such as ASD, ADHD, and developmental delays have aggressive behaviour, limited communication, social and motor skills (American Psychiatric Association, 2013). Acquiring these skills and the knowledge necessary for interacting positively and successfully with peers is a challenge. At the same time, typically developing peers may not know about the functional and cognitive limitations of the disability of their peers. As a consequence, children with disabilities are often socially rejected by their peer group. This may induce changes in spillover effects on parents (French & Waas, 1985; Guralnick, Connor, & Hammond, 1995; Lindsay & McPherson, 2012; Nowicki & Sandieson, 2002; Odom et al., 2006). To some extent, the neighbourhood determines who the peers of a child will be at school and home and the availability of needed health, recreational and social services (Roy, Maynard, & Weiss, 2008).

1.2.3.4.3 Cultural Context (Cultural Beliefs and Religious Beliefs)

Other second-level factors that moderate the spillover effects on parents and family members are the family's cultural contexts. The religious and spiritual values of the family are known to influence informal caregivers' practices and play a significant role in coping with the stress of informal caregiving for persons with chronic illness (Chang, Noonan, & Tennstedt, 1998; Dilworth-Anderson, Williams, & Gibson, 2002; Donovan, Williams, Stajduhar, Brazil, & Marshall, 2011). A few studies have examined the relationships between the family's cultural context and caregiving for a child with chronic illness or disability. Most studies were conducted on caregiving for the elderly population. For instance, some studies have found that religious practices beliefs have motivated family members to provide care to mentally ill relatives (Guberman, Maheu, & Maille, 1992; L. Hinton, Tran, Tran, & Hinton, 2008). Religious beliefs may affect the quality of the relationship between informal caregivers and care recipients (Dishinon & Bullock, 2001). Extended kin support and sense of family obligation may differ between different cultures, thereby affecting the expectation of the care recipient. For instance, in some countries in Asia, family support (providing care to an ill child) is much more prominent than in European countries (Morimoto, Schreiner, & Asano, 2003; Parveen & Morrison, 2009). In addition, community attitudes and beliefs towards a child's chronic illness or disability impact the magnitude of family health spillover effects. For instance, parents who encounter negative attitudes and beliefs in the community may experience stigmatization and isolation from their communities (Bywaters, Ali, Fazil, Wallace, & Singh, 2003; Munyi, 2012).

1.2.3.4.4 Unexpected Crises

Unexpected crises such as pandemics and financial crises can influence the magnitude of family spillover effects. Pandemics such as COVID-19 and H1N1 created many stressors for parents of children with chronic illness or disabilities, including but not limited to community restrictions, loss of childcare, loss of access to recreational and school-based therapies services offered through schools and loss of access to medical care or rehabilitation programs. For instance, during much of the COVID-19 pandemic, most of the schools, parks, and non-emergency medical care (e.g., disability-related medical care, rehabilitation programs, personal care

assistance and other disability-related medical care) were closed. In a survey in Canada, parents (including parents of a least one child with a disability) reported that during COVID-19 lockdowns, children with disabilities were more restricted than children without disabilities (Arim, Findlay & Kohen, 2020). Consequently, children with disabilities and their parents are left out at home isolated, adding a substantial burden on parents. In addition, because of disruption to normal activities coupled with spending more time at home, children with disabilities may experience additional anxiety, depression, and an increase in behavioural problems. Parents of children with ASD reported their children experienced anxiety, depression, and increased in behaviour problems (Colizzi et al., 2020; Cahapay et al., 2020).

Consequently, it can be highly challenging for parents to provide care for children at home, impacting parents' health and well-being. Evidence shows that parents of children with disabilities are more concerned about the impacts of COVID-19 on physical, mental, and social health than children without disabilities (Arim, Findlay, & Kohen, 2020; Majnemer et al., 2021). Furthermore, they were concerned about their ability to manage their child's anxiety, emotions, and behaviours. With the shift to online learning and working from home, parents of children with disabilities may need to performed dual roles. For instance, a study in Canada reported that parents of children with disabilities might need to work additional ten hours per week in assisting with school activities than parents without disabilities (Greenlee, 2020). Further research is required to see how this extra burden will impact the health and well-being of parents. From these reports, it is evident that parents of children with disabilities have to take additional caregiving responsibilities during such expected crises.

1.2.3.4.5 National and Provincial/Territorial Health Policies and Access to Health and Social Care Services

Third level factors of the model that moderate the spillover effects of a child's illness or disability on family members are the national and provincial/territorial health policies and local access to health and social care services. In the Canadian context, federal and primarily provincial/territorial governments play a significant role in providing health and social care services to children. Access to health and social care services depends on federal and provincial

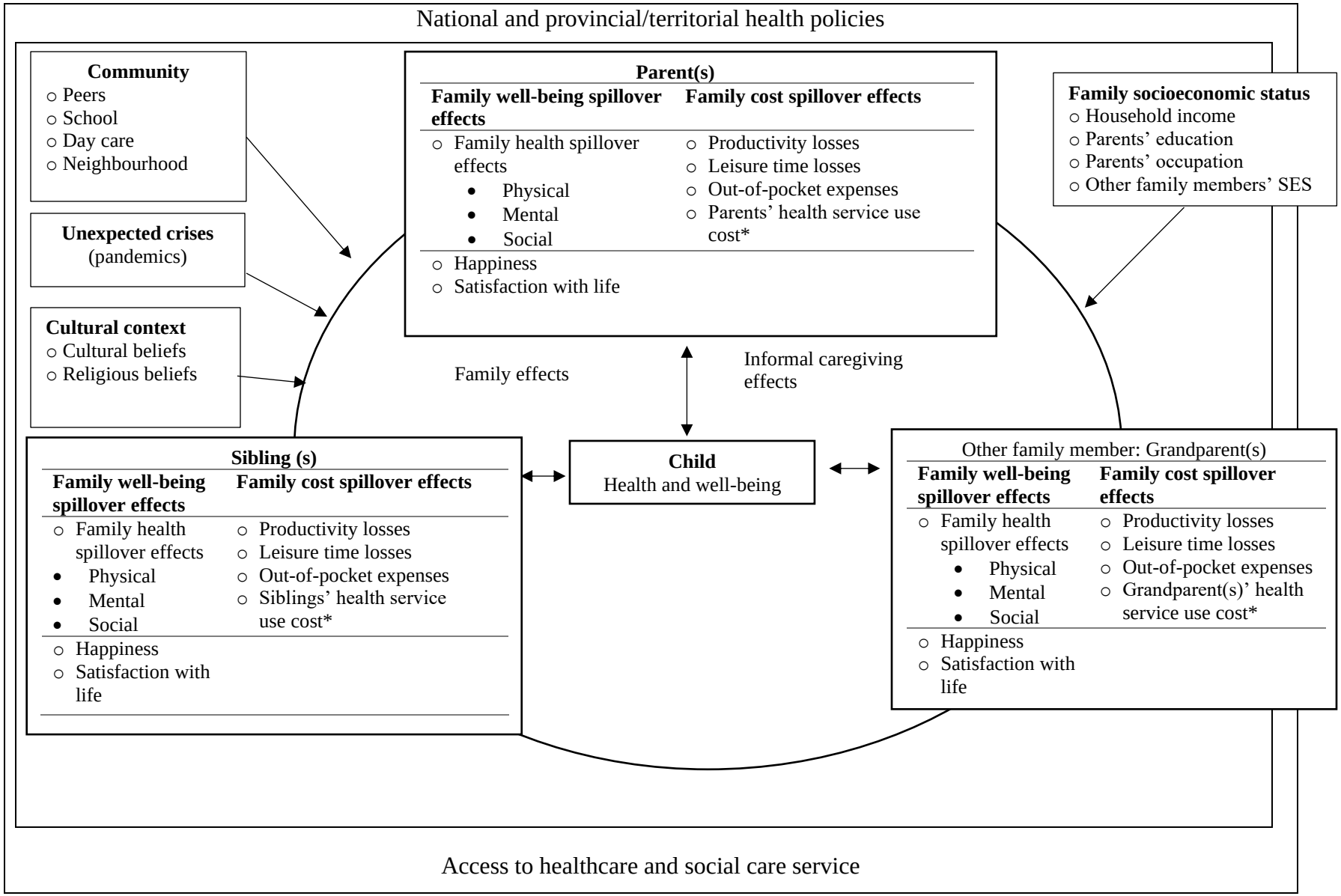
policies. Here, access relates to a family's ability to understand, locate, and connect with the services their child requires. Parents are primarily responsible for the coordination of services for their children as children are not able to decide on their own.

Children with chronic illnesses or disabilities require a wide range of specialized services, often including education, social services, and health services, to enhance their health and development. Learning about a child's needs, finding services to meet these needs, determining eligibility, and deciding who will pay for them can be stressful for parents. These services are supported through multiple ministerial areas: community and social services, health, and education. If parents are not informed with accurate and up-to-date information about programs and services offered, they may have difficulty navigating the system to attain services. Often a challenge for parents is the fragmentation of services provided to support children with chronic illness or disabilities. Because of a lack of consistent policies and inconsistent standards for information sharing across jurisdictions, parents of children with disabilities or chronic diseases may have enormous challenges in navigating and accessing needed support services. Similarly, various programs are designed to provide specialized services for parents and caregivers of children with disabilities. However, often, the availability of such programs varies considerably from one community to another community. Parents may need to move from one service or region to another resulting in higher stress levels, feelings of isolation, and frustration (J. C. Brehaut et al., 2009; Hodgetts, Nicholas, Zwaigenbaum, & McConnell, 2013; Hodgetts, Zwaigenbaum, & Nicholas, 2015).

Marginalized and vulnerable groups such as new immigrants, indigenous communities, rural and remote communities might be more susceptible to spillover effects than other more resilient groups. A review of studies reported increased barriers to healthcare for immigrant families of children with disabilities due to challenges gaining access to and navigating the new healthcare system (King, Lindsay, Klassen, Esses, & Mesterman, 2011). On top of that, new immigrants face additional challenges such as learning a new language and new social rules, finding a new job and adjusting to a new environment and culture, which exacerbate the family spillovers for immigrant parents (Alsharaydeh, Alqudah, Lee, & Chan, 2019; Bradby et al., 2007; Fellin, King,

Esses, Lindsay, & Klassen, 2013). Indigenous families of children with disabilities on and off reservations also face greater barriers in accessing services because of a lack of adequate transportation, mobility, and living arrangements. In a qualitative study, parents of a child with Down Syndrome and health impairments living on a rural reservation indicated that the local public school told them that they do not have the staff to provide educational services for her son, so she would have to take him over 70 miles to the city for school (Banks & Miller, 2005).

Figure 1-1 Conceptual Framework for Family Spillover Effects due to a Child's Illness or Disability



*Cost of parents ‘or siblings’’ or grandparents’ health services use for their own health problems stemming from a child’s illness or disability

Figure 1 presents a conceptual framework for family spillover effects. The definition of family is widespread and varies from discipline to discipline. For this conceptual model, family is defined as: *people living in the same dwelling who are related to a child (≤18 years) with chronic illness or disability by blood, adoption, or foster care and are closely involved in the day-to-day operations of the household and support each other regularly*. The conceptual model has three levels. The first level, inner circle, refers to the process by which a child's health condition generates family spillover effects. There is little guidance on which family members should be included and how to identify these family members. Al-Janabi et al. developed a framework for including spillover effects in 'family networks,' which encompasses the close network of individuals around the patient (Al-Janabi et al., 2016). Canaway et al. used hierarchical mapping alongside in-depth interviews to examine who and how many individuals are close to those at the end of life and could be considered for spillover effects (Canaway, Al-Janabi, Kinghorn, Bailey, & Coast, 2019). The authors suggested focusing on the three closest family members or individuals. That conceptual model focused on three key family member types: parents, siblings, and grandparents. The family spillover effect is likely to be correlated to the strength of the relationship an affected child has with family members. One may expect such effects to be significant for the parents. To date, research has predominately focused on the parents and, to a lesser extent, on siblings and grandparents when assessing the positive or/and adverse effects of a child's health.

The second level of the model depicts the external factors (externalities) that moderate the family spillover effects of illness or disability. These include the socioeconomic status of the family (parents' income, employment status, education, and occupation), community-level factors (peers, school, daycare, and neighbourhood) where a child grows, cultural context (cultural and religious beliefs of the family), and external events (such as the COVID-19 pandemic, H1N1 pandemic, economic recessions). Finally, the third level of the conceptual model refers to the national and provincial health policies and access to health and social care services that influence family spillover effects of illness or disability on family members. The arrows show a

bidirectional relationship, i.e., the family members' health and well-being also affect their children's health and well-being and vice versa.

1.3 Study Rationale and Thesis Structure

The notion that a child's health condition has significant effects on the family's welfare is self-evident. At present, however, family effects are often ignored in pediatric economic evaluations (Lavelle et al., 2019). This lack of inclusion of family spillover effects may be due to the lack of valid and reliable theoretical and empirical for incorporating them into the pediatric economic evaluation. A few theoretical and empirical frameworks for measuring spillover effects, particularly health spillover effects on family members of chronically ill or disabled adults and incorporating them into CEA have been introduced. However, their validity and reliability in child health is unknown, as there is a significant difference between child health and adult health that needs to be considered when considering family spillover effects. Theoretical and empirical work on including spillover effects is in the early stages and requires further research and exploration. The overall theme of this thesis focuses on developing a theoretical framework for incorporating family spillover effects in pediatric economic evaluation, gauging, and examining the existing evidence on theoretical explanations for the inclusion of family spillover effects in pediatric CUA and measuring the health-related quality of life, care-related quality of life, mental health service use and time losses from paid labour and/or usual daytime activities of parents of children with a ND.

Chapter 2 aims to assess and explore the existing evidence on the inclusion of family spillover effects in pediatric CUAs. Two previous reviews have looked at the inclusion of family health outcomes in pediatric and maternal-perinatal CUAs, but neither has focused on how family outcomes were measured, assessed, incorporated and reported. Lavelle et al. reviewed pediatric CUAs published between 2000 and 2015 using the Tufts Medical Center Cost-effectiveness Analysis (CEA) Registry and the Pediatric Economic Database Evaluation (PEDE) Registry (Lavelle et al., 2019). The authors found that out of 142 pediatric CUAs, 105 considered either family costs or health spillover effects. Including family spillover effects tends to make CUA results more favourable. Hulst and colleagues reviewed economic evaluations in obstetric care

published between 2000 and 2018 (Hulst et al., 2021). The authors found a wide variety of methodological choices and low adherence to economic evaluation guidelines for economic evaluation. The authors identified items of economic evaluation guidelines frequently not complied with within obstetric economic evaluations. The authors considered items that are part of reference cases in international cost-effectiveness guidelines, perspective, comparator, type of economic evaluation (analytical technique), time horizon, outcome measured (effects), converting future costs and effects to their present value (discounting) and dealing with unknown information needed for the evaluation (uncertainty). The authors found various methodological choices in terms of 'type of analysis,' 'effect measure,' and 'time horizon' as items of economic guidelines that frequently are not complied with in the context of economic evaluation of obstetric interventions. To date, however, no studies have systematically reviewed how family health spillover effects were measured, assessed, incorporated and reported in maternal-perinatal CUAs. Lavelle et al. documented how family health spillover effects were measured and incorporated but was not comprehensive (Lavelle et al., 2019). The review (i) only included the only CUAs conducted from a societal perspective, (ii) excluded CUAs focused on a prenatal population and (iii) did not include reports published by HTA agencies such as CADTH and NICE (technology appraisals and highly specialized technologies). Moreover, the review lacks a detailed description of how family health spillover effects on parents and/or caregivers or other family members are measured, incorporated, and reported. For instance, the authors did not decision-analytic models and how health outcomes of children and family health spillover effects are combined. The first objective was to determine the methods used to incorporate family health spillovers into pediatric CUAs. The second objective was to describe theories that researchers have used, explicitly or implicitly, to justify the methodological approach to include family spillover effects in pediatric CUAs. The final and third objective of chapter 2 was to determine the methods used to integrate maternal and child health outcomes in maternal- perinatal CUAs. It is important to determine how the health outcomes of family members are measured, assessed, incorporated and reported in pediatric and maternal-perinatal CUAs. Identifying current measurement, assessment, incorporation and reporting methods and their strengths and weaknesses in the literature base can inform best practices in this field moving forward.

Currently, there are several challenges and no standard approach to measuring, assessing, incorporating and reporting family health spillover effects.

Chapter 3 presents a theoretical framework for incorporating family spillover effects in the economic evaluation of the child health intervention. The primary objective was to develop a theoretical framework for incorporating family spillover effects in pediatric economic evaluation using insights and integrating them from identified theories, conceptual frameworks, and models. A further aim was to propose an approach for including family health and cost spillover effects in pediatric CUA based on the theoretical framework.

Chapter 4 measures the HRQoL, care-related quality of life, mental health service use and time losses from paid labour and/or usual activities of parents and/or caregivers of children with a ND. Finally, Chapter 5 summarizes and integrates the key findings of this thesis, discusses their implications for various stakeholders, recommends future research, and ends with concluding remarks.

2 Systematic Review of Methods Used by Pediatric CUAs to Include Family Health Spillover Effects and Maternal-perinatal CUAs to Integrate the Health Outcomes of Pregnant Women and Children

2.1 Introduction

In publicly funded and/or private payer healthcare systems, cost-utility analysis (CUA) is increasingly used in the decision-making process, funding, reimbursement, and pricing of a new pharmaceutical product or intervention. A CUA is a particular type of economic evaluation, where health benefits are expressed in quality-adjusted life-year (QALY) or disability-adjusted life-year (DALY) (Drummond et al., 2015). Both metrics combine the length and the quality of life (QoL) in a single outcome (Sassi, 2006). The QALY-based CUA is recommended by many health technology assessments (HTA) agencies in high-income countries (HICs). For instance, organizations such as the Canadian Agency for Drugs and Technologies (Canadian Agency for Drugs and Technology in Health (CADTH), 2017) and the National and Care Excellence (NICE) (NICE, 2013) responsible for providing information on the efficiency of drugs and medical devices to healthcare decision-makers in Canada and the UK require CUAs of alternative treatments or interventions. The CUA is also the recommended analytic technique in other publicly funded healthcare systems such as in Australia (PBAC, 2016) and the Netherlands (ZorginstituutNederland, 2016). Multiple HTA agencies, in their guidelines on conducting cost-effectiveness analysis (CEA), have recognized the importance of including caregiver (and/or family) spillover effects in the reference or non-reference case analysis. For instance, the 2013 NICE's guide to the methods of technology appraisal states that "For the reference case (National Health Service (NHS) and personal social services (PSS) the perspective on outcomes should be all direct health effects, whether for patients or other people" (page 33) and in the summary of reference case, this expanded as "whether for the patient or, when relevant, carers." (page 32, (National Institute of Health and Sciences (NICE), 2013)). The Canadian guideline states "any associated spillover beyond the targeted population(s), in terms of either costs or effects, should be addressed in a non-reference case analysis." (page 2 (Canadian Agency for

Drugs and Technology in Health (CADTH), 2017). The Second Panel on Cost-Effectiveness in Health and Medicine in the United States (the USA Second panel on CEA), in its 2016 update, recommended adding a societal perspective for the reference case (Neumann, Sanders, Russell, Siegel, & Ganiats, 2016). The societal perspective enables the inclusion of productivity costs of caregivers in the reference case. However, there is no explicit guidance on how family or caregiver health spillover effects should be incorporated into CUAs.

Researchers have also advocated for a fuller inclusion of caregiver and family spillover effects in CUA (Brouwer, 2019; Prosser, Lamarand, Gebremariam, & Wittenberg, 2015; J.M. Tilford & N. Payakachat, 2015; Ungar, 2011; Wittenberg & Prosser, 2013). Family health spillover effects are non-monetary effects (positive or negative effect or both) on the health and wellbeing of family members. These effects stem from *family effects and caregiving effects.* Family effects occur in family members due to witnessing the suffering or worse health state of a loved one such as a child, 'caring about other.' Caregiving effects are health effects in caregivers due to proving care for a child or someone who is ill, 'caring for other' (Bobinac, Van Exel, Rutten, & Brouwer, 2010, 2011; Brouwer, 2019). *Family cost spillover effects* refer to monetary impacts such as productivity costs and out-of-pocket costs for parents and the costs of family members' health or social service use for problems caused by a child's illness (Grosse, Pike, Soelaeman, & Tilford, 2019; Lavelle et al., 2019).

The DALY-based CUA is generally used in low- and middle-income countries (LMICs). DALYs reflect the sum of years of life lost (YLL) due to premature mortality and years lived in disability or disease (YLD) (C. J. Murray, 1994). In the calculation of DALY, each state of health is assigned disability weights on a scale from 0 to 1, whereby '0' represents perfect health and '1' equates to death. The disability weights are multiplied by the number of years lived with disability or disease and added to the number of years lost due to that disease or disability.

Although there is growing recognition of the importance of incorporating family spillover effects in adult and pediatric CUAs of health care interventions, only a very small proportion of published CUAs have included family spillover effects (Goodrich, Kaambwa, & Al-Janabi, 2012; Lavelle et al., 2019; Pennington, 2020). While both the family costs and health spillover

effects represent the effects on family welfare, as per guidelines, researchers have usually considered only the monetary family cost spillover effects, such as productivity losses of parents (caregivers), parents' out-of-pocket costs for transportation or lodging for the child to receive medical and/or non-medical services and parents' out-of-pocket costs or copayments (deductibles) for the child's health in pediatric CUAs conducted from the societal perspective. Indeed, a review of pediatric CUAs conducted from a societal perspective published between 2000 and 2015 found that out of 142 pediatric CUAs, 103 considered the family costs spillover effects and only 15 included caregiver(s) health outcomes (Lavelle et al., 2019). Moreover, a recent review of published NICE technology appraisals of adults and children health interventions found that only 16 of 414 technology appraisals (TA) or highly specialized technologies (HSTs) included the health effects on the caregiver(s) (Pennington, 2020).

This difference in the inclusion of family costs versus family health spillover effects reflects a lack of consensus and standardized methods for measuring, valuing, and including family health spillover effects compared to methods for measuring, valuing, and including family costs spillover effects in pediatric CUAs. It might be also because guidelines on the CUAs do not explicitly recommend including the family spillover effects compared to the inclusion of caregiver time costs in the CUA. The USA Second panel on CEA has acknowledged that methodological and data-related constraints have limited the inclusion of family health spillover effects in adults and pediatric CUAs (Neumann et al., 2016).

2.1.1 Methodological Challenges in Assessing and Incorporating Family Health Spillover Effects in Pediatric Cost Utility Analyses

There exist several methodological challenges in assessing and incorporating family health spillover effects. These include but are not limited to: (1) measuring and quantifying family health spillover effects (Prosser et al., 2015; Eve Wittenberg, Lyndon P James, & Lisa A Prosser, 2019), (2) combining the child and family members' health outcomes (Lavelle et al., 2019; Prosser et al., 2015; Ungar, 2011; Eve Wittenberg et al., 2019), and (3) constructing decision-analytic models that consider costs and health effect of family members (Prosser et al., 2015; Ungar, 2011). These challenges are discussed in detail in the discussion section of this chapter. The following paragraphs briefly describe them. The first challenge is regarding

measuring and quantifying family health spillover effects (Lavelle et al., 2019; Wittenberg & Prosser, 2013). The family health spillover effects should be measured and valued as preference-based health-related quality of life (HRQoL) because the recommended health outcomes in the reference case are QALYs. To date, the most common method of measuring health spillover effects in caregivers and family members is using preference-based HRQoL instruments (Goodrich et al., 2012; Lavelle et al., 2019; Pennington, 2020; Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). Preference-based HRQoL instruments, such as EuroQoL-5 Dimension (EQ-5D), Health Utilities Index Mark 2 (HUI-2), Health Utilities Index Mark 3 (HUI-3), and SF-6D [derived from short form 36 health survey]), were developed to measure the HRQoL of patients (Brazier, Roberts, & Deverill, 2002; Brooks & Group, 1996; Horsman, Furlong, Feeny, & Torrance, 2003). The domains included in these HRQoL instruments may not accurately capture the family health spillovers (Eve Wittenberg et al., 2019). Direct elicitation methods such as the time-trade-off and standard gamble might be an option, but there are several challenges unique to these methods too. The standard gamble measures the utility of a chronic disease health state by observing the willingness to accept a particular risk of death to avoid the state (Drummond et al., 2015; Gafni, 1994). The time trade-off (TTO) is a choice-based method of eliciting utility, reflecting the length of remaining life expectancy that a person may be prepared to trade-off in order to avoid remaining in a sub-optimum health state (Drummond et al., 2015; Matza et al., 2014). For instance, parents may find difficulties in disentangling their own well-being from child's well-being when answering direct elicitation questions such as the time they would be willing to trade-off to improve the child's health. This may lead to double counting the child and parent health (Lavelle et al., 2019; Prosser et al., 2015; Wittenberg & Prosser, 2013).

Secondly, even if there were reliable and valid instruments to measure family health spillover effects of family members, aggregating health utilities across the child and family members elicited through various preference-based HRQoL instruments would be problematic because domains included in the child and family members instruments might be different (Cernat, Hayeems, Prosser, & Ungar, 2021). Moreover, even if there was a single preference-based instrument to measure the HRQoL of the child and family members at different stages of their

lives, it may not be appropriate to combine QALYs because a QALY is defined as a function of QoL and individual life expectancy (Cernat et al., 2021). It is also important to note that there are several challenges in measuring health utilities using current preference-based HRQoL instruments for a child and there is a paucity of preference-based HRQoL instruments for children and none for very young children and infants (Keren, Pati, & Feudtner, 2004; Lamsal, Finlay, Whitehurst, & Zwicker, 2020; Lisa A Prosser, James K Hammitt, & Ron Keren, 2007a; Ungar, 2011).

Finally, if decision-analytic models are needed to be constructed for conducting pediatric CUA with family health spillover effects, it is difficult to determine whether to create a single decision model consisting of all the health states and clinically relevant events to the pediatric patient and the family members, or whether to construct separate decision-analytic models for the child and the family members. Ideally, a decision-analytic model should reflect all the clinical pathways and health states associated with the child and family members while including family spillover effects to estimate unbiased costs and effectiveness of an intervention and comparators (Philips, Bojke, Sculpher, Claxton, & Golder, 2006; Sonnenberg & Beck, 1993). Therefore, using the former approach could be challenging as it might be difficult to identify all the health states and clinically relevant events, and the researchers may need to consider a large number of health states. This adds complexity to the model. It may not be easy to find parameter estimates (transition probabilities between two states, costs and effects associated with various health states). Studies have shown a paucity of HRQoL data on caregiver effects and family effects (Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). Moreover, the question remains whether the health utility of family members, such as a mother, should be included in a child's health state utility, as a separate health state for a mother, or as a combined health state for the child and mother — a "family" health state. The second approach, constructing multiple decision analytic models would be an option. However, there are still associated challenges including combining the estimated QALYs or health utilities from multiple decision models into a single outcome (Cernat et al., 2021; C. J. Murray, 1994; Ungar, 2011).

2.1.2 Measuring and Incorporating Family Cost Spillover Effects in Pediatric Cost-Utility Analyses

Unlike family health spillover effects, family cost spillover effects, such as the productivity losses for missed time at paid or unpaid labour for parents due to a child's illness or disability, can be measured using a diary or recall methods and monetized using the human capital (HC) or friction cost (FC) methods (Drummond et al., 2015; Grosse et al., 2019; Koopmanschap, Rutten, van Ineveld, & Van Roijen, 1995). The HC method considers every hour not worked as an hour lost and calculates productivity costs as the product of those total lost hours with the hourly wage (Grosse et al., 2019; W. Van den Hout, 2010). The FC method only considers the time (hours or days) needed to replace a sick employee with another employee (Koopmanschap et al., 1995).

Parents (caregivers) of children with disabilities or chronic illness can be asked to report how many hours they lost in paid work time during a previous period (day, week, or month) due to caregiving. Similar questions can be asked to the parents of healthy children. Using the HC approach, the costs of productivity losses for the missed time of paid labour due to caregiving for parents of children with disabilities or chronic illness can be estimated by multiplying the total work hours lost due to caregiving with an hourly wage. A similar approach could be used to estimate productivity costs of the missed time of paid labour due to caregiving for parents of healthy children. The differences in estimated the costs of productivity losses for the missed time of paid labour due to caregiving for parents with chronic illness or disabilities and parents of healthy children would give the family cost spillover effects due to missed time at paid work. The premise of the FC method is that an employee who leaves the job can be readily replaced by either someone who is already employed or an unemployed individual (Birnbaum, 2005; Pike & Grosse, 2018; Ungar & Santos, 2003). From the employer's perspective, the relevant factor is the length of time it takes to recruit and train a replacement worker, referred to as the friction period (Grosse et al., 2019; Pike & Grosse, 2018). If a parent (caregiver) of children with disabilities or chronic illness leaves the job due to caregiving responsibilities, the family cost spillover effects due to missed time at paid work would be the costs of productivity lost while a replacement worker is found plus costs to the firm of replacing a parent. The loss of productivity incurred

during the friction period, the time it takes to replace a worker and train their replacement, is often assumed to be 80% of gross production (Krol & Brouwer, 2014; Pike & Grosse, 2018).

For the purpose of pediatric CUA, the productivity costs associated with the missed time at paid or unpaid labour for parents due to caregiving in the treatment and usual care can be measured and valued using similar approaches described above. For example, in a CUA of cognitive-behavioural therapy for treating anxiety disorders in children with autism spectrum disorder, Van Steensel et al. asked parents to report time missed at work for the last three months and estimated the productivity costs using frictional cost methods (Van Steensel, Dirksen, & Bögels, 2014). The time needed to replace a sick employee was assumed to be 160 days. The estimated productivity costs for parents in comparator groups estimate using HC or friction cost methods can be summed with the respective associated costs of the child's health resources to determine the total costs for patients or per family.

2.1.3 Maternal-Perinatal Cost-Utility Analyses

Another area of research where incorporating the health outcomes of the child and the family member (i.e., the mother) is particularly pertinent is CUAs of maternal-perinatal treatments or programs. Maternal-perinatal treatments or programs are delivered during pregnancy, childbirth or immediately after delivery to mothers and fetuses or newborns. Effective maternal-perinatal interventions can have positive effects with significant implications for the long-term health and wellbeing of mothers, newborns, and children (Adam et al., 2005; Lassi et al., 2014). In some cases, these interventions can have a profound impact on reducing maternal and neonatal mortalities (Lassi et al., 2014). For instance, vaccination of mothers against tetanus and influenza reduces maternal and neonatal mortalities (Abu Raya & Sadarangani, 2018; Demicheli, Barale, & Rivetti, 2015; Naleway, Smith, & Mullooly, 2006; Romanin et al., 2020; Tamma et al., 2009). The screening of fetal heart rate during pregnancy can detect congenital heart disease (CHD) which may lead to improved health outcomes for neonates (Verdurmen et al., 2016). Similarly, smoking cessation during pregnancy has been shown to reduce preterm birth and low birth weight and provides long-term benefits for women (Lumley et al., 2009; Schneider, Huy, Schuetz, & Diehl, 2010). Nutritional interventions such as folic acid and iron supplementation

for women during pregnancy in low-income countries have been correlated with long-term health benefits for the woman and the healthier development of the fetus (Peña-Rosas & Viteri, 2009; Yakoob & Bhutta, 2011). Therefore, it is necessary to consider the health outcomes of both the mother and child in perinatal CUAs to understand the full impacts of treatments or programs on health and wellbeing.

However, like in pediatric CUAs, health consequences for both pregnant women and fetuses, neonates, perinates, or infants are included infrequently. Hulst et al., 2020 recently reviewed economic evaluations of treatments or programs in obstetric care. The researchers found that 34% (28/82) measured maternal and neonatal QALYs as the health outcome measure (S. Hulst, Brouwer, Mol, & van den Akker-van Marle, 2020). In another review of economic evaluation of maternal health services (maternal and newborns) published between January 2000 and September 2019 in LMICs, only three CUAs out of 48 considered the effects on both maternal and newborn health (Mangham-Jefferies, Pitt, Cousens, Mills, & Schellenberg, 2014).

The abovementioned methodological challenges that have constrained the incorporation of the family health spillover effects in pediatric CUAs are also pertinent for CUAs of maternal-perinatal interventions (Png et al., 2021; Simon, Petrou, & Gray, 2009). In addition, a unique challenge for CUAs of maternal-fetus interventions is how to measure, value and incorporate fetal losses in composite measure health outcomes such as QALYs or DALYs (S. Hulst et al., 2020; Png et al., 2021; Simon et al., 2009). Because of this unique challenge, miscarriages and/or stillbirths are not commonly included as health gains or losses in CUAs of maternal-perinatal interventions (Petrou, 2001; Simon et al., 2009). Despite these methodological challenges, it is essential to include the health outcomes of both the mother and child in CUAs to measure and value the full health and wellbeing impacts of maternal- perinatal interventions on the family and society.

2.2 Research Objectives

As described above, there are numerous methodological challenges in measuring and valuing the family health spillover effects and there is a lack of standardized methodologies for incorporating family health spillover effects compared to measuring and valuing the family cost

spillover effects in pediatric and perinatal CUAs. Researchers have usually considered the family cost spillovers effects, such as productivity losses for parents and parents' out-of-pocket costs for child's health in pediatric CUAs conducted from the societal perspective. Therefore, this review focused on the family health spillovers and did not consider the family cost spillover. The study objective was to summarize methodologies used to integrate the health outcomes of the child and family member(s). This study aimed to: (i) determine the methods used to incorporate family health spillovers into pediatric CUAs, (ii) identify theories that researchers have used to justify the methodological approach to include family spillover effects in pediatric CUAs, and (iii) determine the methods used to integrate maternal and child health outcomes in maternal-perinatal CUAs.

2.3 Methods

2.3.1 Data Sources and Search Strategy

A systematic review of the literature was carried out to identify articles that included family cost or health spillover effects or both in pediatric CUAs, and health outcomes of the mother and child in perinatal CUAs. A search of the following six electronic databases covered literature from inception to 16 November 2020: MEDLINE, Embase, EconLit, Cochrane collection, Cumulative Index to Nursing and Allied Health Literature and, Internal Network of Agencies for Health Technology Assessment). A comprehensive search strategy was developed using search terms identified from published literature reviews combining search terms to identify economic evaluations (cost-effectiveness and cost-utility analyses) and neonates, newborns, infants, children, and adolescents (Lavelle et al., 2019; Ungar & Santos, 2004). A supplementary search examined the Pediatric Economic Database Evaluation (PEDE) for potentially eligible studies (Ungar & Santos, 2003). The pediatric economic evaluations studies (published between 1980 and 2019) included in the PEDE database are selected from a search of a broad range of databases and over 70 health technology assessment (HTA), academic and government websites. A second supplementary search was conducted whereby a single researcher (RL) manually searched reference lists of included studies to identify eligible studies. The same inclusion criteria described for databases were applied in both supplementary searches. Articles generated

by all database searches were compiled using Endnote X8.2. The search strategy for MEDLINE is provided in Appendix A.

2.3.2 Study Selection

Inclusion criteria were applied in two stages. In the first stage, titles and abstracts were screened by a single researcher (RL). Studies were retained during the first stage if a review of the title, abstract, and keywords indicated that the study included participants who were aged 18 years of age or younger (perinate, neonate, infant, child, and adolescent), and health outcomes were measured in QALYs or DALYs. The requirement for studies to be published in a peer-reviewed journal and written in English was incorporated at this first stage. Studies or reports published by HTA agencies such as CADTH, NICE and the Institute for Clinical and Economic Review (ICER) were also included. After title and abstract review, a single researcher (RL) acquired the full text of identified articles. The second stage involved the hierarchical application of inclusion and exclusion criteria. First, studies were excluded if study participants, or an identifiable subsample, were not neonates, infants, children, or adolescents (≤18y). Second, studies were excluded if studies were not original CUAs, i.e., economic evaluations that did not use QALYs or DALYs to quantify health benefits. Randomized controlled trials, observational studies and modelling studies were eligible. Finally, studies must have included the health spillover effects or cost spillover effects or both for one or more family members in analyses for review of methods of inclusion (objective i). Family member(s) is defined as a person living in the same dwelling related by blood, adoption, or foster care to a child, and who is closely involved in the day-to-day activities of the household and support the child regularly. CUAs of interventions before birth or during or relating to pregnancy (perinatal interventions) and targeted toward pregnant women or fetuses or neonates or perinates or infants were included if health outcomes were measured in both the mother and fetuses, neonates, or perinates or infants. For the purpose of maternal-perinatal CUAs, the fetus is defined as an unborn offspring, from the embryo stage until birth), the neonate is newborns, until the first month of age), the perinates (antenatal period of the fetus or premature newborn, up to seven days of life) and infant (one month to one year of age).

2.3.3 Data Extraction and Analytic Consideration

The following descriptive data was extracted independently by a single researcher (RL) using a standardized data collection form from studies that met the inclusion criteria: 1) bibliographic information including researchers and year of publication; 2) country of population; 3) disease/condition; 4) participants, 5) aim/objective of the study; 6) perspective and time horizon, and 7) intervention(s) and comparator(s). Furthermore, the following information was extracted from the pediatric CUAs: 1) family health spillover outcome; 2) family health spillover measured in family member(s); 3) instrument used in family members to measure family health spillover effects; 4) instrument used in child to measure utility; 5) the magnitude of health spillover effect reported by researchers; 6) modelling approach; 7) methods used to integrate family health spillover effects, and 8) type of family cost spillover effects. The family health spillover effects could include health effects for parents, siblings, and extended family members.

For the purpose of this study, family health spillover effects were defined as the impact of a child's illness on the HRQoL of family members. This could be expressed as a family member's QALY loss, DALY loss, utility, disutility, or an increment in utility. The family member disutility associated with a child's chronic illness or disability is derived by subtracting the utilities for a health state of parents of a child with chronic illness or disability from a health state of parents of a healthy child (Wittenberg & Prosser, 2013).The family cost spillover effects include: (i) productivity costs associated with loss of employment or reduced working hours or loss unpaid labour or usual activities , or loss of leisure time due to caregiving, (ii) out-of-pocket costs or co-payments for health resources for the child's health, (iii) out-of-pocket costs for transportation and lodging for the child to receive healthcare and non-healthcare services such as social services, rehabilitation, education, and others, (iv) household expenditures related to the child's illness or disabilities and (v), cost of medical and non-medical services used by a father and mother for their health and wellbeing as a direct result of caring for a child with chronic illness or disability.

The following additional information was extracted from the included maternal-perinatal CUAs: 1) health utilities or disability weights or QALYs or DALYs of pregnant women and fetuses,

neonates, perinates and infants and 2) the methods researchers used to combine the health outcomes of fetuses, neonates, perinates and infants and pregnant mothers.

The number of pediatric CUAs that considered family cost spillover effects or family health spillover effects was counted. The methods used to integrate family health spillover effects into analyses were tabulated and described. Further goals were to determine the number of maternal-perinatal CUAs studies that have included the mother and child's health outcomes and to describe how these health outcomes were integrated into the analyses. The health conditions/diseases were categorized by the International Classification of Diseases 11 revision (ICD-code) chapters for description purposes (WHO, 2019).

2.3.4 Quality Appraisal

The Quality of Health Economic Studies (QHES) instrument was used to assess the quality of included pediatric CUAs and maternal-perinatal CUAs (Ofman et al., 2003). The QHES was developed to evaluate the appropriateness of the methodology, the validity and transparency of the study results and the comprehensiveness of reporting the study itself. The QHES scale includes 16 items. Each question is scored as "yes" or "no," with each "yes" answer being added to the total score. Each item receives a weighted score ranging from 1 to 9 points totaling 0 to 100 points. An economic evaluation with score ≥75 is considered high quality and <75 poor qualities. The QHES instrument has been widely used to evaluate the quality of economic evaluations (Min, Xue, Haotian, Jialian, & Lingli, 2021). The QHES is included as Appendix C. A single reviewer used the QHES to assess the quality of each included cost-utility analysis. Five pediatric CUAs (NICE TA and HSTs) were not included in the quality appraisal because the complete reports are not available to the public.

The study's primary objective was to review the methods used by researchers to consider family health spillover effects in pediatric CUAs and combine the health outcomes of pregnant women and children in maternal-perinatal CUAs. Currently, there are no standard guidelines on methodology to incorporate family health spillover effects and integrate the health outcomes of pregnant women and children. Furthermore, there are not any quality assessment tools or instruments to evaluate the quality of methods used to incorporate family health spillover effects

and integrate the health outcomes of pregnant women and children. As such pediatric and maternal-perinatal CUAs were not excluded based on the quality appraisal. The strengths and weaknesses of different approaches used by researchers are presented in the discussion section of this chapter.

2.4 Results

2.4.1 Search Results

Figure 2-1 illustrates an overview of the search and retrieval processes. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to report the search results (Moher, Liberati, Tetzlaff, & Altman, 2010). The literature resulted in 27,070 articles. After duplication was removed, 24,395 articles were eligible for the first-stage review. The first stage review of titles and abstracts excluded 23,471 articles. The primary reasons for exclusion were targeting non-pediatric populations or non-pregnant women, and the use of non-preference-based health outcome measures or health outcomes that were not QALYs or DALYs. The full texts of 924 remaining studies were accessed for the second stage of screening. Out of 924, 146 studies were CUAs of maternal-perinatal treatments or programs, and 778 studies were CUAs of pediatric treatments or programs. Of 778 CUAs, 276 CUAs studies met the inclusion criteria and 648 CUAs studies were excluded because they were not pediatric or were not in -pregnant women or included adult populations (n=26) or were not CUAs studies (n=12) or did not include the health spillover effects or cost spillover effects or both or health outcomes of the mother and child (n=610; maternal-perinatal CUAs=101 & pediatric CUA=509). Out of 139 CUAs of maternal-perinatal treatments or programs, 38(27%) included health outcomes of the mother and child in analyses. Similarly, out of 747 pediatric CUAs, 20 (3%) included the family health spillover effects, and 235 (31%) considered the family cost spillover effects in analyses. The most common family cost spillover effects included were productivity cost due to loss of employment or reduced working hours and out-pocket costs for transportation. A search of the PEDE database yielded four pediatric CUAs studies that considered the family health spillover effects. An additional five pediatric CUAs that included family spillover effects were identified through manual reference searching of included CUAs studies and previous reviews.

Furthermore, seven maternal- perinatal CUAs that included health outcomes of the mother and child were identified through manual reference searching and previous reviews. Thus, data was extracted from 29 pediatric and 45 maternal-perinatal CUAs.

2.4.2 Study Characteristics

Table 2-1 summarizes each of 29 pediatric CUAs included in the systematic review by country of population, disease/health condition, age of participants, aim/objectives of the study, perspective, time horizon, intervention, and comparator. Most pediatric CUAs focused on infectious and parasitic diseases (n=15, 51%), with gastroenteritis being the most common disease studied (n=11). Other conditions included mental, behavioural, or developmental disorder (n=5), disease of the nervous system (n=2), disease of the ear or mastoid process (n=2), endocrine, nutritional, or metabolic disorders (n=2), disease of the immune system (n=1), disease of the musculoskeletal system or connective tissue (n=1), and certain conditions originating in the perinatal period (n=1). Vaccines were the most common intervention type (n=17, 59%). Twelve (41%) of the CUAs that considered the family health spillover effects were conducted from the societal and healthcare system perspectives, followed by healthcare system perspective (n=7), societal perspective (n=7), mother and neonatal perspective (n=1) and not stated (n=2). Eight (n=8, 27%) of the included studies adopted a lifetime horizon. The United Kingdom was the country where most (n=9, 31%) of the studies were conducted. The details on the characteristics of pediatric CUAs can be found in Appendix D.

A summary of study characteristics of 45 maternal-perinatal CUAs included in the systematic review is provided in Table 2-2. Out of 45 maternal-perinatal CUAs, 35 (78%) were QALY-based CUAs, and the remaining 10 were DALY-based CUAs. Most of maternal-perinatal CUAs focused on maternal infectious and parasitic diseases or fetus and newborn affected by maternal infectious and parasitic diseases (n=18, 40%), followed by delivery (n=6), diabetes mellitus in pregnancy (n=6), maternal and neonatal death (n=3), congenital maternal heart disease affecting fetus or newborn (n=2), disease of the circulatory system (n=1), diseases of appendix (n=1), maternal care for known or suspected abnormality of pelvic organs (n=1), maternal care for suspected macrosomia (n=1), postpartum hemorrhage (n=1), fetus or newborn affected by

maternal use of tobacco (n=1), labor and delivery complicated by vasa previa (n=1) and other diseases (n=3). Screening/diagnostic was the most common intervention type studied (n=14, 31%). The majority of interventions or treatments were targeted for pregnant women (n=12, 26%). Other target populations were pregnant women and perinates (n=7), pregnant women and neonates (n=6), neonates (n=5), fetuses (n=4), perinates (n=2), infants (n=2), pregnant women, neonates, and infants (n=2), pregnant women and fetuses (n=2), pregnant women and children (n=1), neonates and infants (n=1), and sexually active women (n=1). Nineteen (42%) maternal-perinatal CUAs undertook the societal perspective, 16 undertook the healthcare system perspective, three undertook healthcare system and societal perspectives, and seven did not state the analysis's perspective. Most of the maternal-perinatal interventions adopted a lifetime horizon (n=32,71%). The United States was the country where most (n=24, 53%) of the maternal-perinatal CUAs were conducted. The details on the characteristics of pediatric CUAs can be found in Appendix E.

2.4.3 Quality of Included Studies

Based on the QHES instrument, seven out of 24 (29%) pediatric CUAs were categorized as poor quality with scores of 75 and below, whereas 17 (71%) pediatric CUAs were categorized as good quality with scores of 75 and above (Table 2-3 and Appendix F). The mean (SD) QHES score was 90.35 (4.76) for 17 pediatric CUAs that met the criteria for high quality (QHES > 75). The mean (SD) QHES score was 69.71 (60.07) for seven pediatric CUAs that met the criteria for poor quality (QHES < 75). The majority of the maternal pediatric CUAs did not discuss the direction and magnitude of potential biases and an explicit rationale for the discount rate. Model-based economic evaluation usually combines the cost and (health) outcomes data from different sources and integrates them into the model. Biases could occur if the data used for the model are not an adequate choice and could impact the results (Adarkwah, van Gils, Hiligsmann, & Evers, 2016; Wijnen et al., 2016). Selection bias can occur if the study participants of studies from where cost and outcome data were derived are systematically different in their characteristics from the target population of the economic evaluation. Most of the maternal-perinatal studies included in this review used data from observational studies and did not discuss the potential bias of studies from which input parameters were sourced. Cross-sectional studies are limited in

establishing temporal associations between exposure and the disease or conditions. A cross-sectional study design that cannot identify temporal changes might estimate family health spillover effects by counting changes in family members' health unrelated to caregiving and thus incorrectly characterized as the family health spillover effects. Furthermore, if the treatment effectiveness input data are not based on randomized controlled trials, it will be challenging to establish if an observed change in family members' health (change family health spillover effects) is due to the child's treatment or intervention (change spillover effects). The observed association may not be causal. This could lead to an over- or under-estimation of the cost-effectiveness of the intervention or treatment. The input data from large meta-analyses or RCT reduce the risk of bias and increase the potential for causal inference, particularly when considering the effects of a child's illness on a mother's health outcomes or vice-versa. Furthermore, a structural assumption bias could occur if a model structure is inconsistent with a coherent theory of the condition being investigated (Adarkwah et al., 2015). The treatment pathways must reflect the underlying nature and process of the disease and a natural or established process of family spillover effects on family members.

The quality scores of 45 maternal-perinatal CUAs ranged from 60 to 94 points on the QHES scale. Sixteen out of 45 (36%) maternal-perinatal CUAs were categorized as poor quality with scores of 75 and below, whilst 29 (64%) were categorized as good quality with scores of 75 and above (Table 2-4 and Appendix G). The mean (SD) QHES score was 89.44 (6.20) for 29 maternal-perinatal CUAs that met the criteria for high quality (QHES > 75). The mean (SD) QHES score was 70.18 (3.67) for 17 maternal-perinatal CUAs that met the criteria for poor quality (QHES < 75). The most common limitations of included maternal-perinatal CUAs were no discussion of limitations and direction and magnitude of potential biases, no clear statements of model assumptions, and using estimates (cost, utilities, and probabilities) from weak sources such as expert opinions.

2.4.4 Methods of Inclusion of Family Health Spillover Effects in Pediatric CUAs

There are primarily three steps in incorporating the family health spillover effects in pediatric CUAs, such as (1) identifying and deciding which family members should be included, (2)

measuring and estimating family health spillover effects, and (3) integrating family health spillovers in analysis. The following sections are described in this sequence.

2.4.4.1 Family Health Spillover Effects Measured in Family members

The first step in incorporating family health spillover effects is identifying family members and deciding which family members should be included in the analysis. Most pediatric CUAs included in this review considered the family health spillover effects on one parent and/or caregiver (n=21, 72%). Appendix H summarizes the types and number of family members and/or caregiver included in pediatric CUAs. Two pediatric CUAs examined the family health spillover effects on two caregivers in reference case analyses (Gabriel Chodick et al., 2009; M. Jit & W. Edmunds, 2007). Similarly, two pediatric CUAs considered the family health spillover effects on one caregiver in the reference case analysis and two caregivers in the sensitivity or scenario analyses (Richard J Milne & Keith Grimwood, 2009; Newall, Beutels, Macartney, Wood, & MacIntyre, 2007). Only two pediatric CUAs included family health spillover effects on family members who were not caregivers (H. Christensen, Trotter, Hickman, & Edmunds, 2014; NICEHST7, 2018). Christensen et al. incorporated the impact of meningitis sequelae on family and network members (H. Christensen et al., 2014). In an appraisal submitted to NICE, strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID), the company included the QALY loss to a family due to the premature death of a child (NICEHST7, 2018). However, both pediatric CUAs did not specify the relationship of family members to the child and the number of family members. Finally, one pediatric CUA considered the family health spillover effect on one caregiver in their original submission to the NICE, three caregivers in a revised submission, and two in the evidence review group analysis (NICEHST3, 2016). Parents, and often mothers, are the primary caregivers for children with illness or disabilities. However, most of the included pediatric CUAs did not identify who the caregiver(s) was (were), a father or a mother or both (equal caregivers) or other family members, except for two pediatric CUAs, which identified a mother as a primary caregiver (Creswell et al., 2015; Partridge et al., 2015).

2.4.4.2 Type of Family Health Spillover Effects Measured in Pediatric CUAs

The second step in incorporating family health spillover effects is to measure and estimate the family health spillover effects. The types of family health spillover effects measured in pediatric CUAs included in this review were heterogeneous. The details on types of family heath spillover effects measured in pediatric CUAs is provided in Table 2-5 and Appendix H. Broadly, these can be categorized into (1) an inherent approach and (2) an isolated approach of measuring family heath spillover effects. *An inherent approach* of measuring family heath spillover effects involved assessment of each family members' current health state or assessment of a current dyad health state (for instance, parent-child dyad in the health state or caregiver-child dyad in the health state). The measurement methods for this approach include measuring the health utilities of family members, QALY of family members, or assessing a dyad health utility. The health utilities of the current health state reflect family members' current HRQoL and, therein, family health spillover effects due to a child's illness or disability. Elderly parents, who are caregivers, are likely to have chronic health conditions simultaneous with their caregiving responsibilities; therefore, their health utility scores will reflect a combination of both effects. The QALY of family members reflects the length of life and HRQoL of family member, therein, family health spillover effects due to a child's illness or disability. Finally, assessing a dyad health utility of a current health state reflects the HRQoL of two individuals within a family, therefore, family health spillover effects (parent-child dyad or caregiver-child dyads).

Alternatively, *an isolated approach* measuring family heath spillover effects involves assessing family health spillover separately. This consists of estimating only the effects of a child's illness or disability on the health utilities of each family member separately. Measurement method for this approach includes measuring family health spillover effects as an isolated quantity in individual family members. For example, utility increments or decrements (disutility) on a parent utility (utility is the number that describes the health state of the parent) or QALYs due to a child's health condition.

Pediatric CUAs included in this review have used both measurement approaches. The majority of included pediatric CUAs used *an isolated approach* to measure family health spillover effects

(n=20, 69%). Eight pediatric CUAs used *an inherent approach* of measuring (n=8, 27%) and one study used the General Health Questionnaire-12 (GHQ-12) to assess mental health in parents (Ulfsdotter, Lindberg, & Mansdotter, 2015).The General Health Questionnaire (GHQ-12) consists of 12 items, each assessing the severity of a mental problem over the past few weeks using a 4-point scale (from 0 to 3) (Pevalin, 2000). The researchers used an algorithm developed by Serrano-Aguilar et al. (Serrano-Aguilar et al., 2009) to convert the GHQ-12 scores into health states values of EQ-5D and, then into QALYs.

Out of 20 pediatric CUAs that took an isolated approach, QALY loss for the caregiver(s) due to a child's illness or disability was the most common type of measurement of family health spillover effects included in analyses (n=10, 50%), followed by disutility of a child's illness or disability on the caregiver(s) (caregiver disutility) (n=5) (NICEHST2, 2015; NICEHST3, 2016 ; NICEHST8, 2018; NICETA373, 2015; Tu et al., 2014), QALY loss of the caregiver-child dyad (n=3) (O'Brien et al., 2009; Prosser et al., 2011; Prosser et al., 2004), family QALY loss due to premature patient death (n=1) (NICEHST7, 2018) and QALY loss of family and network member due to child's illness or disability (n=1) (H. Christensen et al., 2014). The caregiver-child dyad QALY loss represent pain and suffering of the child and parent and the family's inconvenience from the disease in a single number. This approach considered a joint QALY loss to both the caregiver and the patient together, rather than valuing them separately and then adding QALY together.

Of eight pediatric CUAs that used an inherent approach, seven pediatric CUAs measured family spillover effects in terms of the health utility of caregiver(s) and one pediatric CUA used health utility of the caregiver-child dyad (n=1) (Hugues Melliez et al., 2008). The health utility of the caregiver-child dyad represents the combined current health states of both caregiver and child.

The instruments developed by EuroQol Group (EQ-5D, EQ-5D-5L, EQ-5D-3L) were the most frequently used instruments to measure the family health spillover effects (n=16, 55%). Other instruments like HUI-2, AQOL-8D and other utility elicitation methods such as time trade-off or visual analog scale or standard gamble were used much less frequently. Christensen et al., in their analysis, assumed that the QALY loss of family and network members due to the impact of

meningitis sequelae was equivalent to 48% of the QALY loss experienced by the meningitis survivor (H. Christensen et al., 2014), referencing a unpublished study by Al-Janabi et al (Al-Janabi et al.). Al-Janabi et al. conducted a UK-wide prospective cross-sectional study of 1600 individuals to someone who had survived meningitis. The researchers estimated QALY losses of the family network by measuring QoL of family members and determined that 48% of the QALY losses of the meningitis survivor. The study by Al-Janabi and colleagues did not measure the impact of death on family members' quality of life. So, Christensen et al. added 9% of a child's QALY loss for the bereaved family and network members using evidence of the impact of bereavement on parents' quality of life from a study by Song et al. (Song, Floyd, Seltzer, Greenberg, & Hong, 2010). Song and colleagues examine the long-term effects of child death on bereaved parents' HRQoL by comparing HRQoL of 233 couples who had experienced a child death with 229 comparison couples whose children were alive at the time of survey. Another pediatric CUA (NICEHST7, 2018) used 9% of a child's QALY loss for the family who lost a patient due to the premature death by referencing Christensen et al. (H. Christensen et al., 2014).

2.4.4.3 Modelling Approach and Integration of Family Health Spillover Effects in Pediatric CUAs

2.4.4.3.1 Modelling Approach used in Pediatric CUAs

The final step in incorporating the family health spillover effects is integrating family health spillover effects in pediatric CUAs. The details on methods of integration of family health spillover effects in pediatric CUAs are provided in Appendix H. Table 2-5 summarizes the various approaches used by researchers for integrating family health spillover in pediatric CUAs. Decision-analytic and statistical models were constructed to incorporate the family health spillover effects and conduct CUAs of pediatric interventions or treatments. Fourteen (48%) pediatric CUAs were performed using decision-analytic models with a Markov decision analytic model most common (n=6), and the remaining fourteen pediatric CUAs used statistical models and one pediatric CUA was conducted using time-trade-off method (Prosser et al., 2004). Of the 14 decision-analytic pediatric CUAs, 13 were conducted using a single decision-analytic model consisting of health states and clinical events relevant to the child defined by different parameter values. Furthermore, in 13 of 14 pediatric CUAs, utility increments or decrements or health

utilities or QALYs lost of caregivers or family members were associated with the child health state (patient disease severity or conditions). For instance, in Australia, in a CEA of rotavirus vaccination, Newall et al. constructed a Markov model to compare no vaccination (usual care) with a vaccination program (with either Rotarix or RotaTeq) (Anthony T Newall et al., 2007). The model followed a hypothetical cohort of children over the first five years of life with a cycle length of one month. The researchers constructed health states relevant to child health, and the outcomes of rotavirus were hospitalization, emergency department visits, general practitioner visits and death. In each cycle of the model, the child remains in one of the health states, to which costs and utilities are assigned. All patients enter the model at birth in a state of being at risk of infection with rotavirus and can transition through health states over time. The researchers assigned an initial 0.9892 utility for the child. If a child gets infected and hospitalized, a loss of 0.00386 QALY (QALY loss for the child due to hospitalization and QALY loss for the primary caregiver due to the child's hospitalization) was deducted in the reference case analysis. For each child in a hypothetical cohort, the total cost and health outcomes were determined by accumulating the costs and utilities associated with each specific health state over the five years of time horizon. In another CUA of rotavirus vaccination in Canada, Coyle and colleagues compared three strategies for preventing rotavirus in children: no vaccination, vaccination with RotaTeq and vaccination with Rotarix (Coyle et al., 2012). The researchers also constructed a Markov model that followed a cohort of children from birth to five years of age with a cycle length of one month. Children enter the model at birth in a state of being at risk of infection with rotavirus and can transition through a number of health states over time. The health states within the model included first infection, recovered from first infection, second infection, not at risk and death. The disutility of a child's illness or disability on the caregiver was subtracted from the child's health utility for the child who got infected with rotavirus.

In contrast, in one pediatric CUA, caregiver disutility of a child's illness or disability on the caregiver was associated with the treatment (NICETA373, 2015). In an appraisal submitted to NICE, the company assigned a disutility of a child's illness or disability on the caregiver for patients based who received treatments (abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis in pediatric patients). The researchers assumed that caregiver

disutility for patients on treatments is half the size of the caregiver disutility for patients not on treatment.

In the remaining one pediatric CUA of resuscitation of neonates at 23 weeks gestational age, Partridge and colleagues constructed two decision-analytic models, one comparing universal resuscitation with no resuscitation, and the second comparing selective resuscitation with no resuscitation (Partridge et al., 2015). The universal model begins with two strategies: universal versus non-resuscitation of live-born infants born between 23 0/7 and 23 6/7 weeks gestation. The newborn could die in the delivery room or admit to NICU. If the newborn survives in the NICU, there could be four outcomes: intact, mild sequelae, moderate impairment, or severe disability. The selective resuscitation model inserts a prior chance node for the probability of delivery room resuscitation where researchers assumed interventions would be utilized only for those infants assessed as likely to have the most favourable outcomes. For bothmodels, Partridge et al. estimated the health utilities for mothers (caregivers) and children, and the mean total QALY for mothersand children were calculated separately and then, the mean total QALY for caregivers and children were summed. For instance, the researchers assigned maternal health utilities of 0.90 and 0.75 for the child with mild sequelae and the child with severe disability, respectively. Further, the researchers assigned neonatal health utilities of 0.69 and 0.23 for the child with mild sequelae and the child with severe disability, respectively. Furthermore, these health utilities were applied to discounted (at 3%) life expectancies to generate maternal QALYs and neonatal QALYs. A combined and separate total QALY gains or losses for caregivers and children due to the treatment were reported separately for two decision-analytic models.

2.4.4.3.2 Integration of Family Health Spillover Effects in Pediatric CUAs

The details on methods of integration of family health spillover effects in pediatric CUAs are provided in Appendix H. Table 2- 5 summarizes the various approaches used by researchers for integrating family health spillover in pediatric CUAs. The approach to integrating family health spillover effects differed among pediatric CUAs. Overall, 19 (65%) pediatric CUAs incorporated the family health spillover effects on caregivers and/or family members in the reference case analyses, and the remaining ten pediatric CUAs incorporated the family health spillover effects

on caregivers and/or family members in the sensitivity or scenario analyses. Of those 19 pediatric CUAs that incorporated family health spillover effects in the reference case analyses, three (16%) pediatric CUAs estimated utilities separately for caregivers and children, and the mean total QALY losses or gains due to the treatment for caregivers and children (treatment effects) were estimated separately. The mean total QALY losses or gains due to the treatment are reported separately for caregivers and children (Chatterton et al., 2019; Creswell et al., 2015; De Kinderen et al., 2016). For instance, in a CUA of stepped care for the management of childhood anxiety disorders, Chatterton et al. assessed the health utility of children using the Child Health Utility – nine-dimension (CHU-9D) and of caregivers (parents) using the Assessment of Quality of Life – eight-dimension (AQOL-8D) at baseline and 12-months follow-up (Chatterton et al., 2019). The estimated health utility was then multiplied by the duration of time spent in a particular health state to estimate separate QALYs for children and parents. The researchers used the area under the curve to assess total QALYs gained by treatment for children and caregivers separately. The area under each curve is the sum of the quality weight for the various health states on the curve multiplied by the duration of each health state. The area between the two curves is the number of QALYs gained by the treatment. The area under the curve equates to the total QALY value with and without treatment (Whitehead & Ali, 2010). Without the treatment, the HRQoL of the individual would reduce over time until they die. If an individual receives treatment, the HRQoL of the individual deteriorates more slowly and lives longer.

In three pediatric CUAs, the mean total QALY losses for caregivers and children were estimated separately, and then the mean total QALY losses for caregivers and children were summed (Gabriel Chodick et al., 2009; M. Jit & W. Edmunds, 2007; Richard J Milne & Keith Grimwood, 2009). A combined mean total QALY gains or losses for caregivers and children due to the treatment was reported. For instance, in a CUA of rotavirus vaccinations in the UK, the researchers summed QALYs losses for the child and two caregivers (0.0018 QALY loss for each caregiver) to calculate the QALYs loss for each episode of rotavirus gastroenteritis that occurred in the reference case (Gabriel Chodick et al., 2009). The number of rotavirus episodes was calculated by adding estimates for the number of general practitioner (GP) consultations, accident, and emergency (A&E) ward admission and nosocomial infections.

Three pediatric CUAs included QALY losses for caregiver-child dyad —a combined estimate of caregiver and child health state (O'Brien et al., 2009; Prosser et al., 2011; Prosser et al., 2004). However, researchers used different methods for inclusion. Prosser et al. asked parents of children with complex otitis media (ear infection) to report the portion of their remaining life they would give to prevent reoccurrence of complex otitis media in their child (Prosser et al., 2004). Parents could choose any amount of time in days, weeks, months, and years. The amount of time the parent is willing to trade the remaining life expectancy was used to estimate QALY loss due to complex otitis media. The estimated QALY loss (parent-child dyad QALY loss) represent impacts of complex otitis media on the children and parent- a dyad QALY loss. For example, if a parent was willing to trade seven days to prevent recurrence of complex otitis media in their children, this represented a one-time loss of 0.02 QALYs. Two others pediatric CUAs used these estimates to measure the parents' pain and suffering related to children's acute otitis media and the impacts of children's influenza-related diseases on parents (O'Brien et al., 2009; Prosser et al., 2011). Prosser et al. included health spillover effects on parents (QALY losses for parent-child dyad) in the model as a one-time decrement in utility for the respective child's health state (Prosser et al., 2011). For instance, an episode of influenza results in a one-time loss of 0.005 QALY for the parent-child dyad. The researchers reported the mean total QALY gains or losses for caregivers and children. O'Brien and colleagues, in another pediatric CUA, constructed a microsimulation model with a monthly cycle to estimate the CEA of current and candidate vaccines against otitis media (O'Brien et al., 2009). The health states include well, acute otitis media (AOM), medically attended (OME), and tympanostomy-tube insertion. If a child experiences an episode of AOM or OME or tympanostomy-tube insertion, associated QALY loss for parent-child dyad was applied. For instance, a loss of QALY (a parent-child dyad) of 0.011 was applied for an episode of AOM. The researchers reported a combined total QALY gains or losses for caregivers and children.

Three pediatric CUAs, estimated health utilities separately for caregivers and children, and the mean total QALY gains or losses for caregivers and children due to the treatment were calculated separately, then, the mean total QALY gains or losses due to the treatment for caregivers and children were summed (Partridge et al., 2015; Tubeuf, Saloniki, & Cottrell, 2019;

Ulfsdotter et al., 2015). A combined and separate mean total QALY gains or losses due to the treatment for caregivers and children were reported. For example, in the economic evaluation of family therapy for self-harming adolescents, Tubeuf et al., estimated health utility of children (aged 11–17 years) using EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L) and of parents using HUI-2 (Tubeuf et al., 2019). And, then researchers estimated separate total QALYs losses or gains for adolescents and caregivers using regression analyses and area under the curve approach. Tubeuf and colleagues first modelled the health utility of parents as a function of the adolescent's health utility and health-related and demographic characteristics of both the adolescent and the parent. The health utilities for adolescents and parents were measured at baseline, six months, and 12 months. The estimated coefficient of an adolescent's health utility is used to measure a spillover coefficient of an adolescent's health utility on parents. Secondly, the estimated parameters of adolescents' health utility at baseline, six months and 12 months were transformed into a QALY gain using the area under the curve approach. Finally, the total QALYs losses or gains due to the treatment for caregivers and children were summed. A combined and separate total QALY gains or losses due to the treatment for caregivers and children are reported.

Three pediatric CUAs estimated the mean total QALY losses for caregivers and children separately, and then the mean total QALY losses for caregivers and children were summed (Bilcke, Van Damme, & Beutels, 2009; A. T. Newall et al., 2007; Shim & Galvani, 2009). A combined and separate mean total QALY gains or losses for caregiver and children due to the treatment reported. For instance, in a CUA of rotavirus vaccination in Australia, the researchers assigned an initial 0.9892 utility for the child. If a child gets infected and hospitalized, a QALY loss for the child due to hospitalization (0.00186 QALY loss) and QALY loss for the primary caregiver due to child's hospitalization (0.00200) were summed and applied (subtracted) to the associated health state in the reference case analysis (A. T. Newall et al., 2007). Bilcke et al., estimated mean total QALY losses for caregiver and children separately, and then the mean total QALY losses for caregivers and children were summed (Bilcke et al., 2009). A combined and separate mean total QALY gains or losses for caregivers and children due to the treatment reported. Notably, the QALY loss for the caregiver was not included in analyses from the

societal perspective. The researchers stated that the QALY losses for the caregiver are implicitly included in the costs of work time loss, and therefore, it might lead to double counting of the health spillover effects on caregivers.

In two pediatric CUAs, caregiver utility decrements or disutilities were subtracted from the child health utility, and the mean total QALY gains or losses due to the treatment estimated and reported only for children (NICEHST2, 2015; NICEHST3, 2016). In these studies, caregiver utility decrements were applied to child health state to represent the caregiver burden. For instance, in an economic evaluation of ataluren for treating children with Duchene muscular dystrophy, the company included caregiver disutility for three caregivers in its reference case for the non-ambulatory patient's. A disutility of 0.33 was subtracted from the child's health utility who in the non-ambulatory health states and that there were no impacts on caregivers of ambulatory child. The disutility 0.33 represented the disutility of three caregivers, two primary caregivers (with the full disutility) and two secondary carers (with half the disutility).

In one pediatric CUA, the researchers estimated utilities for caregivers and child-dyad and a combined mean total QALY gains or losses for caregivers and children due to the treatment calculated and reported (H. Melliez et al., 2008). Melliez and colleagues attributed a dyad health-utility (utility of 0.884 in case of mild rotavirus diarrhea and 0.816 in case of severe diarrhea) to a child and one caregiver per child based on Seneca et al. study results (Seneca et al., 2006). Finally, the remaining pediatric CUA estimated utilities separately for caregivers and children, and utilities of caregivers and children were summed to estimate the mean total QALY losses or gains for caregivers and children due to the treatment (Schawo et al., 2015). A combined mean total QALY gains or losses for caregivers and children due to the treatment was reported.

Of those ten pediatric CUAs that incorporated family health spillover effects in the sensitivity or scenario analyses, mean total QALY losses for caregivers or family network members or family QALY losses due to patient premature death were summed or applied (in some studies authors are not explicit about how they combined the QALY losses of caregivers and children) with the child QALYs losses in six pediatric CUAs (Bilcke, van Hoek, & Beutels, 2013; H. Christensen et al., 2014; Hansen Edwards, de Blasio, Salamanca, & Flem, 2017; NICEHST7, 2018; Tilson et

al., 2011; Tu et al., 2012). In four pediatric CUAs, the disutility or utility decrements for one caregiver due to child's illness was subtracted from the child health utility within in health states to represent the caregiver burden in scenario or sensitivity analyses (Coyle et al., 2012; NICEHST8, 2018; NICETA373, 2015; Tu et al., 2014). For instance, in a NICEHST8 appraisal of burosumab for treating X-linked hypophosphataemia in children and young people, the company modelled the caregiver disutility by patient's disease severity (NICEHST8, 2018). The disutility of 0.08 was subtracted from the health utility of the child in the moderate and severe health states up to the age of 18 years in the scenario analysis.

Finally, out of 29 pediatric CUAs that have included family health spillover effects, only one study used theories to justify its methods of inclusion (Tubeuf et al., 2019). Tubeuf and colleagues proposed the quantification methods for incorporating the parental health spillover effects based on household welfare function and an equivalence scale (ES) to generate a health gain within the family to sum to the adolescent's QALY gain (Buhmann, Rainwater, Schmaus, & Smeeding, 1988). The household welfare theory states that individual welfare entails a family welfare function. The welfare of each family member can be aggregated to measure the family as a whole welfare function to make comparisons between households (Buhmann et al., 1988). The concept of ES has been used in economics to measure social welfare and adjusts the income of all household members accounting for the size of the household and the age of its members (Buhmann et al., 1988; Tubeuf et al., 2019). The researchers state ES allows them to adjust all health gains for the rest of the household as an additional individual equivalent QALY or utility gain where all the household members are accounted for.

2.4.5 Methods of Integration of Health Outcomes of Pregnant Women and Fetuses, Neonates, Perinates and Infants in Maternal-perinatal CUAs

There are primarily two steps in incorporating health outcomes of pregnant women and children in maternal-perinatal CUAs, such as (1) measuring and estimating the health outcomes of pregnant women and children and (2) integrating the health outcome of pregnant women and children.

2.4.5.1 Methods Used to Measure Health Outcomes of Pregnant Women and Fetuses, Neonates, Perinates and Infants

This section synthesizes methods researchers have used to measure the health outcomes of pregnant women and children. Appendix I shows the details on methods of integration of health outcomes of pregnant women and fetuses, neonates, perinates and infants. Fetuses, neonates, perinates and infants will be referred to as 'children' from here onwards for reporting/summarising purposes. Table 2-6 summarises the methods used by researchers for combining the health outcomes of pregnant women and children. Most of QALY-based maternal-perinatal CUAs 22 out of 35 (62%) measured health utilities as health outcomes of pregnant women and children separately. Moreover, three QALY-based maternal-perinatal CUAs measured QALY loss of pregnant women and children due to the disease separately (Danyliv et al., 2016; Diane Farrar et al., 2016; VanDeusen, Paintsil, Agyarko-Poku, & Long, 2015), two QALY-based maternal-perinatal CUAs measured disutilties associated with the disease of pregnant women and children separately (Gilbert, Grobman, Landon, Spong, et al., 2013; Gilbert, Grobman, Landon, Varner, et al., 2013), two QALY-based maternal-perinatal CUAs measured disutilties associated with diseases and QALY of pregnant women and children separately (Mrus, Goldie, Weinstein, & Tsevat, 2000; Schackman, Oneda, & Goldie, 2004), one QALY-based maternal-perinatal CUA measured QALYs of pregnant women and children separately (Mrus & Tsevat, 2004), one QALY-based maternal-perinatal CUA measured QALY and QALY loss of pregnant women and children due to the disease separately (B. Y. Lee, Bailey, Wiringa, Assi, & Beigi, 2009), one QALY-base maternal-perinatal CUA measured QALY loss of pregnant women and children due to the disease and disutilites associated with the disease for pregnant women and children (van Hoek, Campbell, Amirthalingam, Andrews, & Miller, 2016). One maternal-perinatal CUA measured the health utilities of children and disutilities associated with disease for pregnant women (Jones, Smith, Lewis, Parrott, & Coleman, 2019) and one maternal-perinatal CUA measured QALY for pregnant-child dyad (n=1). In a CUA of screening strategies for antenatal diagnosis of visa Previa in singleton pregnancies, Sinkey & Odibo assigned 17 QALY for the maternal-neonatal dyad for the mother to live without morbidity and for the infant to survive, 16.9 QALY for the maternal-neonatal dyad for the mother to live with morbidity and for the infant to survive, 15.3 QALY for the maternal-neonatal dyad for the

mother to live without morbidity and for the infant to die and 15.2 QALY for the maternal-neonatal dyad for the mother maternal morbidity dies and infant dies. These estimates were derived from a study by Cipriano and colleagues (Cipriano, Barth Jr, & Zaric, 2010). In their analysis, Cipriano et al. used age-adjusted baseline health utilities for women and infants from another study (Manuel & Schultz, 2004) and calculated QALYs maternal-neonatal dyad. The HRQoL of mothers was reduced if delivery-associated morbidity occurred or in the instance of a late fetal or neonatal death. Cipriano et al. assumed that maternal morbidity results in a utility reduction of 15% in the year of delivery, followed by a return to the age-adjusted values (Cipriano et al., 2010). Late fetal or neonatal death results in a utility reduction for the mother of 24% for the next eight years based on a study of disutility for fetal death associated with invasive prenatal testing. One maternal-perinatal CUA measured the health utility and disutilites for pregnant women and children separately (Jones et al., 2019). Finally, the remaining one maternal-perinatal CUA measured health utility of a pregnant women-child (n=1) (Culligan et al., 2005). The health care providers (expert panel) assigned the health utilities for each mother and newborn clinical scenario. For instance, an expert panel assigned the health utility of 0.995 for vaginal delivery, including 1st or 2nd-degree episiotomy that heals normally and healthy child, health utility 0.5 for a mother with anal incontinence and healthy child, and 0.35 for the child with severe permanent brachial plexus injury in a child and anal incontinence in mother.

Most of the QALY-based maternal- perinatal CUAs did not estimate or incorporate or were unclear regarding how researchers valued or incorporated the fetal losses (miscarriages and stillbirths) in CUAs. Of those that did, a utility value of 0 was assigned to fetal losses (C. M. Albright, Werner, & Hughes, 2019; Bak et al., 2020; P. Y. Chen et al., 2016; E. K. Clennon, Pare, Amato, & Caughey, 2019; Emily K Clennon, Pare, Amato, & Caughey, 2021; Kaimal et al., 2011; Ohno et al., 2011; Elisa Sicuri et al., 2011). Furthermore, some studies estimated the fetal losses as a QALY loss and incorporated in the analysis (Diane Farrar et al., 2016; Round et al., 2011). For instance, in a CUA of screening strategies for gestational diabetes mellitus, Round and colleagues assigned a QALY loss of 25 QALYs for a stillbirth, which is an approximation of the QALYs accrued over a life expectancy of 80 years in a perfect health discounted annually (Round et al., 2011).

The majority of QALY based maternal-perinatal CUAs did not consider or were unclear regarding the impacts on pregnant women related to the loss of the fetus or neonate in women who experiences a miscarriage or termination or fetal losses for any other causes. Of those studies that did, a utility value of 0.92 was assigned to mother who experiences a miscarriage or stillbirths or fetal losses for any other causes (Bak et al., 2020; P. Y. Chen et al., 2016; Emily K Clennon et al., 2021; Danyliv et al., 2016; Hersh, Megli, & Caughey, 2018; Kaimal et al., 2011; Little & Caughey, 2005; Mistry & Gardiner, 2013; Ohno et al., 2011), referencing a study by Kuppermann et al (Kuppermann et al., 2000). Kuppermann and colleagues used a standard gamble to estimate the maternal health utility for pregnancies that ended in loss of the fetus. The researchers asked pregnant women what probability of death they would accept to avoid a specific health outcome, such as down syndrome. It is interesting to note that two QALY based maternal-perinatal CUAs used 0.76 for maternal health utility for neonatal and infant death and 0.92 for fetal losses (Emily K Clennon et al., 2021; Hersh et al., 2018). However, time horizons for disutility or utility decrements applied to mother associated with the fetal losses varies among studies. Some QALY based maternal-perinatal CUAs applied utility decrement or disutility associated with the fetal losses across the remainder of maternal life whereas some studies applied utility decrement or disutility for a few years. For instance, one QALY-based maternal-perinatal CUA assumed miscarriage would reduce the maternal QoL for one year and fetal demise would reduce the maternal quality of life for two years (Hersh et al., 2018). In another CUA, the researchers assumed that neonatal or intrauterine death would reduce the maternal QoL for the next 10 years and miscarriage would reduce the maternal QoL for the next two years (Bak et al., 2020). Furthermore, it is important to highlight that no QALY-based maternal-perinatal CUAs included the impacts of a loss of mother during pregnancy on the child.

Most of the QALY-based maternal-perinatal CUAs derived health outcome values for pregnant women and children from published studies that used various preference-based HRQoL instruments or other health utility elicitation methods. For example, time trade off, standard gambles, EQ-5D, HUI-2, researchers' or experts' assumptions were used for pregnant mothers. Similarly, HUI-2, time trade-off, standard gamble, researchers', or experts' assumptions, were used for fetus, neonates, infants, perinates and children. Therefore, it was difficult to summarise

and compare preference-based HRQoL instruments or other utility elicitation methods used among included maternal-perinatal CUAs.

On the other hand, the common method used by 10 DALY-based maternal-perinatal CUAs to assess health outcomes of pregnant women and children was measuring DALYs averted of pregnant women and children separately (n=9, 90%) (Adam et al., 2005; Babigumira et al., 2012; Choi, Brandeau, & Bendavid, 2017; Goodman et al., 2017; Jo et al., 2019; Kuznik et al., 2012; Lubinga, Atukunda, Wasswa-Ssalongo, & Babigumira, 2015; Orenstein et al., 2017; Prinja et al., 2018; E. Sicuri et al., 2010). For instance, in CEA of intermittent preventive treatment of malaria in pregnancy, Sicuri et al., calculated DALYs averted per neonates by multiplying the number of neonatal deaths averted by the number of DALYs lost due to neonatal mortality (E. Sicuri et al., 2010). Similarly, DALYs averted per mothers was calculated by multiplying the number of DALYs maternal deaths averted by the number of DALYs lost due to the disease by the reduction of malaria morbidity and mortality as a result of the intervention.

2.4.5.2 Modelling Approach and Integration of Health Outcomes of Mothers and Fetuses, Neonates, Perinates and Infants

2.4.5.2.1 Modelling Approach in Maternal-perinatal CUAs

Appendix I shows the details on methods of integration of health outcomes of pregnant women and fetuses, neonates, perinates and infants. Fetuses, neonates, perinates and infants will be referred to as ‘children’ from here onwards for reporting/summarising purposes. Table 2-6 summarises the methods used by researchers for combining the health outcomes of pregnant women and children. All but two maternal-perinatal QALY-based CUAs (33, 97.05%) were conducted using a single decision model consisting of health states and clinical events relevant to the pregnant women and children defined by different parameter values. For instance, in the US, Kastenberg et al., constructed a decision analytical model and a Markov model to compare the following strategies: diagnostic laparoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) (Kastenberg et al., 2013). A hypothetical cohort of 25-year-old prim gravid women in the second or third trimester of pregnancy with a valid concern for appendicitis and the child (after the birth) were followed for a lifetime. The pregnant women enter one of

these strategies. If women received laparoscopy, it could result in either a positive appendectomy or negative appendectomy, whereas computed tomography and MRI results in either a positive or negative scan, which then leads to either an operation or no operation. The women, then, undergo either expedited operation resulting in no perforated appendicitis, a negative appendectomy, a delayed operation with perforated appendicitis, or no operation. The surgical outcomes include no complication, complication, or death. The researchers assumed that maternal death results in fetal death. For surviving mothers, the subsequent fetal outcomes include full-term delivery, pre-term delivery, or fetal death. Surviving children enter a Markov model to capture the risk of developing radiation-associated childhood acute lymphoblastic leukemia. To determine the QALY, the utility value associated with a given state of health was multiplied by the years lived in that state across the lifetime of the mother and child. The total QALY gained or losses by each strategy was calculated by summing of QALY gains or losses for pregnant women and children.

Two maternal-perinatal QALY-based CUAs were conducted by constructing two decision analytic models (Elisa Sicuri et al., 2011; Wymer, Shih, & Plunkett, 2014). In cost-effectiveness of a trial of labor accrues with multiple subsequent vaginal deliveries, Wymer and colleagues constructed separate decision analytic models for the maternal and neonatal outcomes (Wymer et al., 2014). A hypothetical cohort of women with one previous full-term and low-transverse caesarean delivery and neonates after trials of labor after caesarean delivery (TOLAC) or (elective repeat caesarean deliveries) ERCD were followed for their lifetime. The outcomes included in maternal model were transfusion, hysterectomy, thromboembolism, intensive care unit admission, end metritis, and death. The neonatal outcomes included respiratory distress syndrome, brachial plexus injury, cerebral palsy, mental retardation, neonatal intensive care unit (NICU admission), and death. A separate QALY gains or losses for the mother or neonate were calculated by respective estimated utility values and life expectancies. The researchers estimated and reported QALY gains or losses separately for pregnant women and children. In a CUA of Chagas disease screening of pregnant Latin American women and of their infants Sicuri et al. constructed two decision analytic models (Elisa Sicuri et al., 2011). One decision-analytic model focused on the newborn. The newborn model compared the option of undertaking the test with

the possibility of not undertaking any test in the mother and, if she is positive, in the newborn. The model then only considered the costs and benefits of an early diagnosis and the consequent treatment of newborns. The second model focused on the mother. The mother model considered the option of undertaking the test against the possibility of not undertaking it. The model then only considered the costs and benefits of an early diagnosis and the consequent treatment of mothers. A separate QALY gains or losses for the mother or newborn were calculated by respective estimated utility values and life expectancies.

2.4.5.2.2 Integration of Health Outcomes of Mothers and Fetuses, Neonates, Perinates and Infants in Maternal-perinatal CUAs

Appendix I shows the details on methods of integration of health outcomes of pregnant women and fetuses, neonates, perinates and infants (referred to as 'children'). Table 2-6 summarises the methods used by researchers for combining the health outcomes of pregnant women and children. The most common method used by researchers for integrating health outcomes of pregnant women and children in maternal-perinatal QALY-based CUAs was to estimate health utilities separately for pregnant women and children, and the mean total QALY for pregnant women and children due to the treatment were summed (n=17, 48%). These studies reported a combined mean total QALY gains or losses for pregnant women and children due to the treatment. For instance, in the CEA of caesarean delivery on maternal request (CDMR) in comparison to the trial of labor (TOL) for prim gravid women, Xu et al. constructed a decision tree consisting of 249 chance events and 101 parameters to reflect the most relevant clinic outcomes after each delivery management scheme (CDMR or TOL) throughout the mother and the newborn's lifetime (Xu et al., 2010). All health utilities were applied over the expected lifespan of mothers and neonates, adjusted for disease-relevant states, and discounted per year. Total QALYs for the mother or newborn was estimated by multiplying the number of expected life-years in each health state by the health utility associated with that health state. Xu and colleagues calculated the mean total QALYs by adding both maternal and newborn QALYs. In their decision-analytic model, researchers assumed that the utility of maternal outcomes is independent of the utility for newborn outcomes, i.e., the mother's QoL of life did not influence the child's QoL after the child's birth. For instance, the utility of maternal death and the utility of

a healthy neonate after caesarean delivery were independent such that each future year in the woman's and the newborns' life was counted 0 and 1. Such assumption was made in several other maternal-perinatal QALY-based CUAs (Beigi, Wiringa, Bailey, MarieAssi, & Lee, 2009; Emily K Clennon et al., 2021; Tan, Macario, Carvalho, Druzin, & El-Sayed, 2010). Remarkably, Mistry & Gardiner, in cost-effectiveness of prenatal detection for congenital heart disease (CHD) using telemedicine screening, used the mother's health utility value during pregnancy and the child's health utility value from birth onwards, ignoring the impacts of screening for prenatal detection of congenital heart disease (CHD) on mothers after the birth of a child (Mistry & Gardiner, 2013).

In four maternal-perinatal QALY-based CUAs, the mean total QALY losses for pregnant women and children were estimated separately, and then the mean total QALY losses for mothers and children were summed (Beigi et al., 2009; Danyliv et al., 2016; D. Farrar et al., 2016; VanDeusen et al., 2015). A combined mean total QALY gains or losses for mothers and children due to the treatment was reported. For example, in a CEA of the cost-effectiveness of universal maternal influenza vaccination, Beigi et al., constructed a single decision tree consisting of maternal and neonatal health states related to epidemic and pandemic influenza characteristics (Beigi et al., 2009). The pregnant women of median age of 27.1 years enter the model and have the option of being vaccinated against influenza. The pregnant women who got vaccinated could experience acute side effects from the vaccine, including but not limited to injection site irritation, fever, and myalgia. Furthermore, pregnant women could develop influenza based on the efficacy of the vaccine. Then, pregnant women who got influenza can stay at home for self-treatment or a clinic visit for the evaluation and/or be hospitalized for more severe illness. The researchers assumed that only hospitalized women have a probability of death. At the time of hospitalization, the gestational age determines the fetus's survival if the mother dies after hospitalization. The development of influenza infection in the neonate was independent of maternal influenza, i.e., even if the mother did not develop influenza, the neonate could develop influenza. However, neonatal probability of influenza was modified by maternal influenza vaccination status. Neonates whose mothers had been vaccinated had a decreased probability of influenza compared to unvaccinated mothers. Neonates who developed influenza had a chance of

hospitalization for severe disease, and only hospitalized neonates were at risk for death. The baseline utility in a pregnant woman was 0.92 and 1.0 for a neonate. The respective QALY loss for pregnant and neonates was deducted as pregnant women, and neonates move through health states.

In three maternal-perinatal QALY based CUAs, utilities were estimated separately for pregnant women and children, and the mean total QALYs were estimated separately for pregnant women and children. The mean total QALY gains or losses due to the treatment were reported separately for pregnant women and children (Hoshi, Seposo, Okubo, & Kondo, 2018; Nicholson, Fleisher, Fox, & Powe, 2005; Wymer et al., 2014).

Furthermore, in two maternal-perinatal CUAs, disutilities associated with the disease were estimated for pregnant women and children separately and the mean total QALYs for pregnant women and children were summed (Gilbert, Grobman, Landon, Spong, et al., 2013; Gilbert, Grobman, Landon, Varner, et al., 2013). A combined mean total QALYs gains or losses for pregnant women and children due to the treatment was reported. For instance, the cost-effectiveness of a trial of labor after one previous caesarean delivery (TOLAC), Gilbert and colleagues constructed a single decision analytic model consisting of maternal and neonatal health states. A hypothetical cohort of 100,000 pregnant women and their neonates followed for their lifetime. A pregnant woman enters of one of these two strategies TOLAC or an ERCD. Women in the TOLAC arm can experience either a successful vaginal delivery, require a repeat caesarean during labour, or have a uterine rupture associated with a successful or failed TOLAC. The maternal outcomes and neonate outcomes depended on the outcomes of these strategies. The disutilties or utility decrements associated with maternal, and neonates' outcomes were subtracted from the corresponding heath utilities for pregnant women and children. For instance, if a neonates develop CP, one of the health outcomes for a child, a disutility of 0.44 was assigned.

Two maternal-perinatal CUAs studies estimated the mean total QALY and disutilities associated with the disease separately for pregnant woman and children, and the mean total QALY losses or gains due to the treatment was calculated and reported separately for pregnant women and

children (Mrus et al., 2000; Schackman et al., 2004). One maternal-perinatal CUA estimated total pregnant -women-child dyad QALY (the detail is described above) and a combined mean total QALY gains or losses for pregnant women and children due to the treatment was calculated and reported (Sinkey & Odibo, 2018). As described earlier, in another maternal-perinatal CUAs, Culligan and colleagues estimated health utilities for pregnant women-child dyad (Culligan et al., 2005). A combined mean total QALY gains or losses due to the treatment for pregnant was calculated and reported.

Furthermore, in the economic evaluation of economic value of administering antiviral medications to pregnant women who have come in contact with an infectious individual with influenza, Lee et al., estimated mean total QALY or QALY losses for pregnant women and children separately and then mean total QALY for pregnant women and children were summed (B. Y. Lee et al., 2009). A combined mean total QALY gains or losses for pregnant women and children due to the treatment was reported. For instance, pregnant women who did not experience medication adverse effects or influenza accrued 0.92 QALY. If pregnant women got uncomplicated influenza, a reduction of QALY of 0.65 was applied through the duration of illness, and if a pregnant woman was hospitalized because of influenza, a reduction of QALY of 0.50 was applied to pregnant women for the time of hospitalization. A similar approach was taken for estimating total QALY gains or losses for the child.

One maternal-perinatal QALY based CUA, estimated the mean QALY loss and disutilities associated with the disease were separately for pregnant women and children, the mean total QALYs loss were summed. A total combined mean QALY gains or losses for children and pregnant women due to the treatment was reported (van Hoek et al., 2016). In CEA of smoking cessation interventions in pregnancy, Jones et al. estimated health utilities and disutilities associated with the disease separately for pregnant women and children and the mean total QALYs for pregnant women and children were summed. A combined mean QALY gains or losses due to smoking cessation intervention for pregnant women and children was reported (Jones et al., 2019). One maternal-perinatal QALY based CUA, estimated utilities for pregnant women and children separately and, the mean total QALY for pregnant women and children were summed, and reported a combined and separate mean total QALY gains or losses due to the

treatment for pregnant women and children (Elisa Sicuri et al., 2011). Finally, in the remaining one maternal-perinatal QALY based CUA, Albright and colleagues constructed a single decision analytical model consisting of maternal and neonatal heath states. The researchers estimated utilities separately for pregnant women and children, and the mean total QALY were estimated and total mean QALY gains or losses due to the treatment reported separately for pregnant women and children (A. Albright, 2019).

All 10 maternal-perinatal DALY-based CUAs, estimated the mean total DALY averted by the intervention or treatment for pregnant women and children separately, and then mean total DALY averted for pregnant women and children due to treatment were summed. A combined and/or separate DALY for pregnant women and children were reported (Adam et al., 2005; Babigumira et al., 2012; Choi et al., 2017; Goodman et al., 2017; Jo et al., 2019; Kuznik et al., 2012; Lubinga et al., 2015; Orenstein et al., 2017; Prinja et al., 2018; E. Sicuri et al., 2010).

To conclude the results section, no one of the maternal-perinatal QALY-based or the maternal-perinatal DALY-based CUAs used theories or provided justifications for the methods used to combine the health outcomes of pregnant women and children.

2.5 Discussion

Despite well-established evidence that a child's health condition significantly affects family members' health and wellbeing and/or economic wellbeing, this review found that only a small proportion of pediatric CUAs included family spillover effects. Of those that did, the majority of pediatric CUAs considered family costs spillover effects. Likewise, a few maternal-perinatal CUAs included the health outcomes of both the mother and fetus or perinate or infant. If a health care intervention improves the HRQoL of a child and therefore improves the HRQoL of family members and reduces the time family members need to spend caring for the child. Ignoring the improvement on HRQoL and reduction in caring time of the family members in an economic evaluation underestimates the value of the intervention. It is surprising that only a few pediatric CUAs considered the family health spillover effects and maternal-perinatal CUAs considered the health outcomes of mothers and children when the first US Panel on Cost-effectiveness in Health and Medicine in 1996 encouraged analysts to think broadly about the people affected by the

intervention and include family health spillover effects on family members in sensitivity analysis when they are significant (Gold, Siegel, Russell, & Weinstein, 1996). Similarly, NICE in 2004 encouraged analysts or researchers to incorporate all costs and consequences of investments or interventions in the reference case analysis from a societal perspective (NICE, 2004) .

Considerable progress has been made in understanding, measuring and valuing family health spillover effects in the context of children's and adults' health since the publication of the Original US Panel recommendation 20 years ago and the NICE guideline on CEA in 2004. Yet, there are no clear, practical guidelines on the inclusion of family health spillover effects in pediatric or adult CUAs. For instance, the Second Panel on CEA, in its 2016, recommend analysts to go beyond the Original Panel's recommendation for the societal perspective and to include parent's time costs (lost work time, lost leisure time) and unpaid caregiver time costs in a reference case analysis from a societal perspective (Neumann et al., 2016). Furthermore, explicitly listing them in an Impact Inventory, but the Second Panel on CEA did not or failed to mention the inclusion of family health spillover effects. However, in texts in another chapter, the Second Panel on CEA recognized that excluding family health spillover effects would lead to an underestimate of CEA of the intervention and echoed the Original US Panel recommendation to include HRQoL effects on family members (significant others) in scenario or sensitivity analyses. The Second Panel did, however, acknowledge the methodological and data-related constraints of the incorporation of the family health spillover effects. More importantly, it has contributed more attention to specific challenges of conducting CUA for the child health intervention and associated family health spillover effects. There has been no progress in the NICE guideline on the CEA since 2004 (NICE, 2004). The recent guidelines state that the perspective on outcomes should be all direct health effects for the reference case, whether for patients or other people (carer) but do not offer a practical guideline on how and when to incorporate. The following sections discuss the significant findings from this review.

2.5.1 Family Health Spillover Effects and Pediatric CUAs

Within pediatric CUAs, a wide variety of methods was employed to incorporate the family health spillovers, with many different types of family health spillover effects measured and many

different methods to integrate the family health spillover effects. As mentioned previously, there are primarily three steps in incorporating the family health spillover effects in pediatric CUAs, including identifying and deciding which family members should be included, measuring, and estimating family health spillover effects and integrating family health spillover effects in the analysis. The following paragraphs are described in this order.

Notably, the number of family members included in pediatric CUAs was consistent with one caregiver. Only two pediatric CUAs in this review included QALY losses of other family and network members who were not caregivers but did not specify their relationships to the child and the number of family members (H. Christensen et al., 2014; NICEHST7, 2018). Numerous studies have shown that a child's illness or disability impacts the health and wellbeing of his/her non-caregiving family members, including a parent(s) and siblings (Dey et al., 2019; Reichman, Corman, & Noonan, 2008; Sharpe & Rossiter, 2002). The literature has referred to this effect as 'family effects,' i.e., the effects of caring for a loved one's health and wellbeing (Bobinac, Van Exel, et al., 2010, 2011; Brouwer, 2019). The family effects extend beyond informal caregivers to other family members who are physically present and/or emotionally connected. For instance, a father or a sibling (not an informal caregiver) experiences the family effect. In fact, previous studies have suggested that the family effects as a stronger determinant of HRQoL of family health spillover effects than the caregiving effects and extend beyond a caregiver to other family members (Lavelle, Wittenberg, Lamarand, & Prosser, 2014; Prosser et al., 2015). Excluding family health spillover effects on family members who are not informal caregivers may underestimate the true burden of illness and potential value of pediatric intervention.

There is little guidance on which family members to include in measuring spillover effects, e.g., the non-caregiving parent, sibling(s), grandparents, or other family members. Canaway et al. proposed a qualitative approach to identify family members close to the individual at the end of life. The researchers suggested focusing on the three most immediate family members (Canaway et al., 2019). Al-Janabi et al. suggested focusing on 'family networks,' which include a close network of individuals around the patient (Al-Janabi et al., 2016). In the context of economic evaluation from the societal perspective, Gold et al. state, "In the extreme, through altruism, entire communities can be affected"(page, 67) (Gold et al., 1996). Infectious diseases, such as

gastroenteritis, measles, and pneumonia, are transmitted across children and can infect many children over time. Thus, in the CUA of pediatric vaccines to control these kinds of disease, it may require considering populations in the entire community to get an unbiased estimate of the costs and benefits of vaccines (Gold et al., 1996). Identification of family members is a necessary step in incorporating family spillover effects. Questions on whom to include in the pediatric CUA should be guided by a theory and require ongoing discussions and further research.

The methods used by researchers to measure the family spillover effects vary across studies, and a consensus approach has not yet been reached among researchers. However, these methods can be broadly categorized into inherent and isolated approaches of measuring family health spillover effects. An inherent approach of measuring family health spillover effects involves assessing the current health state of family members, such as measuring a parent's or caregiver's health utility, which reflects the current HRQoL of a parent and, therein, family health spillover effects. The isolated approach of measuring family health spillover effects involves assessing family health spillover effects alone as an isolated quantity, such as measuring utility decrements (or disutility) or increments on a parent due to caring for and caring about component of having a child with chronic illness or disability. The variation in measurement methods of the family health spillover effects may be partially explained by available data on family health spillover effects on family members. For instance, out of 11 pediatric CUAs focused on gastroenteritis, nine measured family health spillover effects in caregiver(s) as a QALY loss due to caregiving, and estimates were derived primarily from one previously published studies (Senecal, Brisson, & Lebed, 2006). A few pediatric CUAs (17%, 5/29) used utility decrements or disutility associated with caregiving estimates applied to the child's utility to capture the family health spillover effects. The infrequency of this approach may be due to the lack of published data on the disutility of patient illness on family members (Wittenberg & Prosser, 2013).

The measurement of utility decrements (disutility) or increments associated with being a caregiver or family member(s) of an ill child, an isolated approach of measuring family health spillover effects, is not much of a focus of the existing literature compared to measuring the health utility of family members or caregivers, an inherent approach of measuring family health spillover effects (Lavelle et al., 2019; Wittenberg & Prosser, 2013). Establishing the causality of

the relationships between a child's health and family members; (caregiver's) health and wellbeing is very complex. For instance, for the parent who provides caregiving, does the strain of providing care lead to a reduction in health and wellbeing on the parent, or does the parent with health problems who becomes a caregiver perceive their care task as being more straining than parents of healthy children? To estimate disutility associated with having a child with chronic illness or disability accurately, one would need to control for caregiver characteristics that affect the utility separate from the child's illness or disability. Researchers have used several methods to isolate the family spillover effects. For instance, Kuhlthau and colleagues compared the EQ-5D scores of parents of children with and without activity limitations to estimate the disutility to parents associated with children's activity limitations (Kuhlthau et al., 2010). In a study evaluating HRQoL changes in informal caregivers, parents of children with major congenital anomalies first rated their current HRQoL on the EQ-VAS. After that, parents again rated their HRQoL for a hypothetical state in which someone would take over their caregiving activities entirely and free of charge. The difference in EQ-VAS scores was considered as disutility to parents associated with having a child with major congenital anomalies.

As noted previously, Christensen and colleagues measured family health spillovers on family and network members as QALY loss, valued at 48% of the child's QALY loss due to meningitis and an additional 9% of child's QALY loss for family and network members if the child is dead (H. Christensen et al., 2014). In one appraisal submitted to NICE, family QALY loss was included as a one-off event due to a premature death and valued at 9% of the child's QALY loss (NICEHST7, 2018) based on Christensen et al study. The latter study did not account for the family health spillover if a child is alive with disease or conditions. Notably, one appraisal submitted to NICE measured family health spillover effects as decrements on the caregiver utility when a child receives a specific treatment. In this study family health spillover effects were linked to the treatment the child received and not to the child's illness (NICETA373, 2015). A caregiver would receive the same magnitude of the family health spillover effects regardless of the size of the benefit the child received from the treatment. Among pediatric CUAs that used an inherent approach in assessing the family health spillover effects, the health utilities of caregivers and/or family members were used to capture the family health spillover effects. The exception

was one pediatric CUA that used a caregiver-child dyad approach whereby the researchers attributed a joint health utilities for a child and one caregiver (Hugues Melliez et al., 2008).

Pediatric CUAs that used health utilities or QALY losses or disutilties to capture the family health spillover effects have used indirect preference-based instruments, such as EQ-5D, EQ-5D-5L, HUI-2, HUI-3, administerd to caregivers and family members to estimate the family health spillover effects. It is important to note that these instruments were designed to measure the HRQoL of patients. The domains included in these instruments may not adequately capture components of HRQoL most relevant to caregivers (Wittenberg & Prosser, 2013). Studies revealed that health spillover extends beyond the caregiver's physical health, and mental and emotional health are domains mostly affected (Al-Janabi, Flynn, & Coast, 2011; Brouwer et al., 2004). For instance, the indirect generic instrument such as EQ-5D measures HRQoL based on five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Although the anxiety/depression domain of EQ-5D contains items about mental health that are the important element of family health spillover effects, EQ-5D may not adequately capture components of HRQoL most relevant to caregivers. New carer-specific instruments, such as the Care-related Quality of Life instrument (CarerQoL) and Carer Experience Scale (CES), have been developed to capture the relevant aspects of the caregiving burden, such as fulfillment and financial problems (W. Brouwer, N. Van Exel, B. Van Gorp, & W. Redekop, 2006b). Albeit these carer-specific instruments are preference-based, these are distinct from QALYs. The CarerQoL and CES include a different and more comprehensive set of domains that are beyond those typically considered in QALY-based measures such as fulfillment, financial problems and relations problems. While they may accurately capture caregiver-relevant dimensions, their valuations are based on a care related quality of life scale so cannot be used to estimate QALYs, and therefore can neither be combined with child health utilities or QALYs (Lavelle et al., 2019; Eve Wittenberg et al., 2019).

Direct elicitation methods such as the time-trade-off, standard gamble and visual analog scale may provide more flexibility in capturing family health spillover effects in HRQoL as they are not elicited based on specific domains (Lavelle et al., 2014; Ungar, 2011; Wittenberg & Prosser, 2013). For instance, using the time-trade-off method, the researchers can ask parents to consider

how much time they would trade-off at the end of their remaining life expectancy to prevent childhood conditions. The amount of time the parent is willing to trade divided by the remaining life expectancy can be used to estimate of QALYs lost due to the condition that incorporates both the impact on the child and the impact on the parent. One parent pediatric CUA in this review used time-trade-off method to estimate QALY loss of the parent-child dyad (Prosser et al., 2004). Prosser et al. asked parents to trade off their own life for preventing a specific number of days of uncomplicated influenza in their child. These estimate were used by two other studies to measure the family health spillover effects on one caregiver (O'Brien et al., 2009; Prosser et al., 2011).

While direct elicitation methods may overcome the drawbacks of indirect methods, researchers have pointed out several challenges that need to be considered when using direct elicitation methods to measure family health spillover effects. For parents, it may be difficult to distinguish their own wellbeing and their child's wellbeing when answering direct elicitation questions, such as the time they would be willing to trade-off to improve the child's health (Lavelle et al., 2019; Wittenberg & Prosser, 2013). Furthermore, it might be difficult for parents to imagine a hypothetically ill child and the impacts of his/her illness on themselves.

It is important to note that most pediatric CUAs that included family health spillover effects mentioned they had included caregiving effects or caregiver effects due to a child's illness or disability. The researchers did not mention whether 'caregiving effects' were restricted to caregiving or also constituted a family effect that also incorporated caring about other effects. In the case of a child with chronic illness or disability, informal caregivers are usually family members. Hence, when measuring family health spillover effects on a family member who is also an informal caregiver, both effects are likely present (Bobinac, Van Exel, et al., 2010, 2011). For example, a mother who is an informal caregiver of a child with autism spectrum disorder can experience both caregiving effects due to performing physically or emotionally demanding care tasks, often over long periods of time, and family effects because of caring about a child such as worrying about a child's health and wellbeing and his/her future (Ezzat, Bayoumi, & Samarkandi, 2017; Vasilopoulou & Nisbet, 2016). Therefore, it is useful to distinguish between family effects and caregiver effects when discussing the family health spillover effects on family

members. The clear differentiation and consistent descriptions of family and caregiving effects in the literature may assist in estimating and including family health spillover effects in pediatric CUAs. It might be challenging to disentangle family and caregiver effects, although some studies attempted to separate family effects and caregiving effects (Bobinac, Van Exel, et al., 2010, 2011).

One of the notable findings of this review was that 34% (10 out of 29) of pediatric CUAs included the family health spillover effects in sensitivity or scenario analyses rather than reference case analyses. The researchers incorporated family health spillover effects in sensitivity or scenario analyses by summing QALY losses of the caregiver(s) and the child or subtracting disutility associated with caregiving from the child's health utility.

Finally, a wide variety of methods were used to integrate and report the family health spillovers in caregivers and family members in reference case or scenario (sensitivity) analyses, as summarized in tables 5 and 7. With such a variety of methods used to incorporate the family health spillover effects in pediatric CUAs, there is no consensus among researchers on how the family health spillover effects should be incorporated in pediatric CUAs. This heterogeneity is mirrored by the lack of practical guidelines by HTA agencies and a theoretical foundation on including family health spillover effects in pediatric CUAs. Evaluating which methods for incorporating family health spillover effects are suitable is not the objective of this chapter. The incorporation of family spillover effects is a relatively new concept in pediatric CUAs, and there are no standard methods of inclusion. Future research should consider developing a critical appraisal tool to evaluate the quality of the methods of incorporating family health spillover effects and the health outcomes of the child and mother. The following paragraphs discuss concerns raised by researchers regarding the methods used to measure and incorporate family health spillover effects into pediatric CUAs. In addition, the following paragraphs discuss our (RL) concerns regarding methods used to measure and consider family health spillover effects into pediatric CUAs included in this review.

Researchers have expressed concerns about some methods used to incorporate the family health spillover effects in pediatric CUAs. The QALY (QALY loss or QALY) summation methods

might not be appropriate for integrating family health spillover effects in pediatric CUA because health utilities used to derive QALYs for the child and family members were measured using different preference-based HRQoL instruments (Cernat et al., 2021; Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). Summing or combining health utilities and QALYs from two different preference-based HRQoL instruments lies in the assumption that two different preference-based HRQoL instruments are of the same nature and meaning and could be combined. For instance, Tubeuf et al. used EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L) for adolescents and HUI2 for a parent to measure the health utilities (Tubeuf et al., 2019). The researchers estimated the separate total QALY gained by adolescents and a parent due to treatment and then combined the total QALYs gains. However, these two preference-based HRQoL instruments are different in descriptive content and valuation technique. While the EQ-5D-3L covers physical, mental, and general health dimensions (EuroQolGroup, 1990) and is valued with TTO HUI2 also considers impairments in vision, hearing, and dexterity and is valued using standard gamble and visual analogue scaling (Feeny, Furlong, Boyle, & Torrance, 1995; Horsman et al., 2003). Furthermore, as abovementioned the validity of calculating spillover QALYs with utilities derived from different current HRQoL instruments remains unknown (Brouwer et al., 2006b; Brouwer et al., 2004; Cernat et al., 2021; Prosser et al., 2007a).

Moreover, it is important to note that preference-based HRQoL instruments currently used, such as EQ-5D-3L used in the above study, in children are developed for adults. There are many challenges in using adults' preference-based instruments in children, where the valuations of health state descriptions are typically elicited from adults (there is a paucity of research for valuations derived from children or adolescents) (Baca, Vickrey, Hays, Vassar, & Berg, 2010; Lamsal et al., 2020; Pickard & Knight, 2005; Prosser et al., 2007a). Children, for whom the most important domains of health may be different, and preference weights for existing domains may also be different (Stevens, 2009). Although in recent years, preference based HRQoL instruments such the youth version of the EQ-5D (ED-5D-Y) (Wille et al., 2010), Child Health Utility 9D (CHU 9D) (Stevens, 2009), have developed or modified for use specifically in children and adolescents. However, there would be still challenges in combing health utilities or QALYs from different preference based HRQoL instruments (adults based and child-based

preference-based HRQoL instruments). Finally, another concern is that QALY is defined and interpreted in terms of an individual's life expectancy (Cernat et al., 2021). It may not be appropriate to combine QALYs between children and family members.

Most of pediatric CUAs that included family health spillover effects were conducted using a single decision-analytic model with a Markov model the most common. These models are comprised of health states only relevant to the child. The family health spillover effects (e.g., utility decrements or increments in a caregiver(s) and family member(s) and QALY loss on a caregiver(s) or a family member(s)) were summed with or subtracted from the health utilities or QALYs or QALY loss of the child health state. Pediatric CUAs that have used the health utility of a caregiver-child dyad and the QALY loss of a caregiver-child dyad to measure and incorporate the family health spillover effects also have constructed a single decision-analytic model that only consisted of health states of a child. For instance, Melliez and colleagues attributed a dyad health utility to a child and one caregiver per child (0.884 in case of rotavirus diarrhea and 0.816 in case of severe diarrhea) and included in the model as the health utility for the respective child health states (H. Melliez et al., 2008). In only one pediatric CUAs, the researchers constructed a two decision analytic models (Partridge et al., 2015). The decision-analytic model should reflect all the clinical pathways and health states associated with the children with chronic illness or disabilities and their family members to estimate unbiased costs and health outcomes.

Based on a close examination of included pediatric CUAs, there are mainly five methodological issues that future researchers could consider to improve family health spillover effects' measurement and incorporation methods. First, most pediatric CUAs included in this review did not consider (or were unclear regarding) family health spillover effects on family members when a patient (child) dies. The death of a child is traumatic for bereaved parents and family members. Studies have reported increasing prescription costs, psychotherapy services and productivity costs among parents following the child's death (N. Dias et al., 2021; Fox, Cacciatore, & Lacasse, 2014; Lichtenthal et al., 2015; van den Berg, Lundborg, & Vikström, 2017). It may be due to the current guidelines on CEA limiting analyses to the duration of the patient’s life expectancy, and grief-related family spillover effects extend beyond this time. Second, no

lifetime horizon pediatric CUAs in this review consider family health spillover effects *shifting*. The time horizon used for a CUA is the duration over which health outcomes and costs are calculated (Drummond et al., 2015). Furthermore, caregivers, often parents, have shorter life expectancies than children within a lifetime study time horizon. Therefore, it is that as a child age and enters adulthood, family health spillover effects shift to their spouse, partner, siblings, or others because of shifting or changing in the role of caregivers. Third, the magnitude of family health spillover effects can be influenced by several factors, such as family members' own health, the health of other family members, socioeconomic characteristics, and others (Chapter 1). Model-based pediatric CUAs need to use the best estimates of family health spillover effects from the literature. Many of the model-based pediatric CUAs (for instance, pediatrics CUAs of rotavirus vaccination) used estimates based on cross-sectional studies, which means it is impossible to determine whether the observed change in parents' and/or family members' health is directly due to a child's illness. Trial-based CUAs that collected data on parents or caregivers have also used poor methods for measuring family health spillover effects. For example, one pediatric CUA regressed the parent utility on adolescent utility to estimate the family health spillovers, ignoring the potential confounding effects of household income (Tubeuf et al., 2019). Fourth, the child's disease or disability is not likely to have an impact to the same extent on all family members (mothers, fathers, siblings) and caregivers (primary, secondary) (Cohn et al., 2020; Langley, Totsika, & Hastings, 2020; Sharma, Singh, Murti, Chatterjee, & Rakkar, 2021; Sharpe & Rossiter, 2002). Four pediatric CUAs in this review included the family health spillover effects on two caregivers (G. Chodick et al., 2009; M. Jit & W. J. Edmunds, 2007; R. J. Milne & K. Grimwood, 2009; Anthony T Newall et al., 2007). However, these pediatric CUAs incorporated the same magnitude of family health spillovers for both caregivers. For instance, Jit and Edmunds et al. used 0.0018 QALY lost for each caregiver per episode of rotavirus gastroenteritis (M. Jit & W. J. Edmunds, 2007). Finally, it may take longer to see the effects of a child's health intervention or treatment on the family members' health outcomes than to see the impacts on the child's health outcome. Family members such as parents may first need to see (experience) the improvement in their child's health due to the health intervention to positively impact their own health. This hypothesis needs to be tested empirically. Current standard practice is to choose the time horizon based on the nature of the disease and the intervention or

treatment under consideration for the CUA. The follow-up time or time horizon is identical for the patient and their caregivers or family members in pediatric CUAs included in this review, which might have underestimated the impacts of the child's health intervention in family health spillover effects. In future pediatric CUAs, analysts may need to consider measuring the health outcomes of family members beyond the follow-up (or time horizon) for patients. The incorporation of family spillover effects is a relatively new concept in pediatric CUA and there are no standard methods of inclusion. The primary purpose of our appraisal of methods was to encourage researchers to develop approaches to address or consider these issues in future analyses to improve the measurement methods and incorporate family health spillover effects.

2.5.2 Health Outcomes of the Mother and Child in Maternal-perinatal CUAs

The majority of maternal-perinatal CUAs measured the health outcomes of pregnant women and children in QALYs compared to DALYs. The results revealed that maternal-perinatal CUAs studies involving lower-income countries more frequently employed DALYs, whereas studies involving higher-income countries are more likely to use QALYs. The lower number of DALYs-based maternal-perinatal CUAs indicates a fewer number of maternal-perinatal CUAs conducted in LMICs.

Similar to pediatric CUAs, researchers used a wide variety of methods to measure and incorporate the health outcomes of the mother and child in maternal-perinatal CUAs. The most common method used to measure the health outcomes of pregnant women and children in QALY-based maternal-perinatal CUAs was using health utility. One QALY-based maternal-perinatal CUAs measured the health utility for pregnant women-child dyad (Culligan et al., 2005) and another study measured the QALY of the pregnant-women-child dyad (Sinkey & Odibo, 2018). These values include a combined estimate of pregnant women and child health state due to a disease or conditions —assessment of a dyad health state for use as a single value in the analysis. The majority of health outcomes values used in QALY based maternal-perinatal CUAs, health utilities, QALY, QALY loss, disutilities or decrement in utilities, of pregnant women and children were derived from several previously published studies. So, it was hard to summarize and compare them. It is noteworthy to mention that in seven QALY based maternal-

perinatal CUAs, the researchers also made their assumptions or used expert opinions to estimate the health utilities of pregnant women or children or both. The researchers justified this approach saying that there is lack of health utilities data in existing literature.

As noted previously, most QALY-based maternal-perinatal CUAs did not consider or were unclear regarding how researchers have valued or incorporated the fetal losses in QALY-based maternal-perinatal CUAs. Of those that did, a utility value of '0' was assigned to fetal loss due to miscarriage or stillbirths or other causes in most studies and a few studies, a QALY loss of 25 QALYs was assigned for a stillbirth or miscarriage. Similarly, most QALY-based maternal-perinatal CUAs did not consider or were unclear regarding the impacts on pregnant women related to the loss of the fetus or neonate in women who experienced a miscarriage or termination. Of those that did, the same utility value of 0.92 was assigned to a mother who experiences a miscarriage or stillbirths in all QALY-based maternal-perinatal CUAs. However, the time horizon for disutility or utility related to fetal losses varies among studies. For instance, some pediatric CUAs applied disutility or utility associated with fetal losses for the next two years of maternal life, while some pediatric CUAs applied disutility or utility associated with fetal losses for the remaining lifespan of the mother (Bak et al., 2020; Hersh et al., 2018; Kaimal et al., 2011).

Moreover, it is important to point out that no QALY-based maternal-perinatal CUAs included the impacts of a loss of a mother during pregnancy on the child. Studies have shown that maternal death during pregnancy can impact the child's health. If the infant survives birth, but the mother does not, the resulting lack of nutrition support from breastfeeding leaves the baby vulnerable to malnutrition and can be fatal or may increase the risk of disease or death from infections (Braitstein et al., 2013; Moucheraud et al., 2015). In the long run, the child may have poor learning outcomes, lower educational attainment, and distrusted living arrangements that can impose trauma that has detrimental impacts on the health and well-being of the child (Hosegood, 2009; O'Donnell et al., 2012). Therefore, it is critically important to measure the impacts on the child due to maternal death and include in maternal-perinatal CUAs to estimate the full value of perinatal treatment or interventions.

In addition, no QALY-based maternal-perinatal CUAs in this review considered the impacts on fathers or partners or other family members related to maternal-perinatal disease or conditions and hence, of maternal-perinatal interventions or treatments. It seems like QALY-based maternal-perinatal CUAs in the review considered pregnancy as a 'women's issue' and ignored the impact of maternal-perinatal conditions on the health and well-being of a father or partner or other family members. For instance, studies have demonstrated that fathers are also affected by the loss of a fetus (Due, Chiarolli, & Riggs, 2017; Miller, Temple-Smith, & Bilardi, 2019; Obst, Due, Oxlad, & Middleton, 2020; Williams, Topping, Coomarasamy, & Jones, 2020). The smoking during pregnancy can cause low bright weight, respiratory distress, preterm birth, and other health problems of infants and affect a mother's health such as miscarriage, premature labour, and other smoking-related illness (Castles, Adams, Melvin, Kelsch, & Boulton, 1999; Cnattingius, 2004; Control & Prevention, 2004). Other children in the family are also exposed to risks associated with the mother's second-hand smoke during pregnancy. Furthermore, there could be adverse effects on spouse or partner health if smoking during pregnancy causes problems for the baby, like premature birth and congenital disabilities. Thus, a smoking cessation program during pregnancy would eliminate adverse effects on the spouse or partner and other children in the family. Therefore, ignoring impacts on fathers or other family members may undervalue the true burden of maternal-perinatal illness and intervention for illness.

Similar to pediatric CUAs, a wide variety of methods were used by researchers to integrate and report maternal and child health outcomes in QALY based maternal- perinatal CUAs as described earlier and summarized in tables 5 and 7. All 10 maternal-DALY based CUAs used a similar method to integrate DALYs of pregnant women and children, which is estimating mean total DALYs averted by the treatment for pregnant women and children separately and then summing up the meant total DALYs averted by the treatment for pregnant women and children and reporting a combined and separate DALYs averted by the treatment for pregnant women and children.

This heterogeneity in methods used by researchers to integrate the health outcomes of pregnant women and children shows there in no consensus among researchers on how the health outcomes of pregnant women and children should be included. All of the abovementioned methodological

challenges in incorporating family health spillover effects in pediatric CUAs are also relevant for maternal- perinatal CUAs.

2.5.3 Summary of Results and Further Research

In summary, only 29 pediatric CUAs included family health spillover effects in the analyses and 45 maternal-perinatal CUAs incorporated the health outcomes of mother and child. The results from this review revealed that it had not been standard practice to include health effects on persons other than individuals directly affected by the intervention in both pediatric and maternal-perinatal CUAs. There is considerable heterogeneity in methods applied to measure family health spillover effects and incorporate them into analyses in pediatric CUAs and in methods applied to measure the health outcomes of pregnant women and children and incorporate them in maternal-perinatal CUAs. The heterogeneity in methods may be due to the lack of standard methods for measuring, valuing, and incorporating family health spillover effects in pediatric CUAs and the health outcomes of mothers and children in maternal-perinatal CUAs. Moreover, this study uncovered those various methods used by researchers for considering the family health spillover effects or combining the health outcomes of pregnant women and children lack a theoretical underpinning.

That some researchers are attempting to address this significant gap in health economics literature in different ways to assess and incorporate the family health spillover effects or incorporate health outcomes of mothers and children in CUAs in encouraging, the inconsistency in approaches and lack of theoretical foundation is concerning as the results of CUAs are less comparable and may have resulted in biased findings and poor policymaking. There is a need to develop a standardized theoretical framework and empirical methods to include the family spillover effects in pediatric CUAs. One way to move forward is by establishing a separate reference case for fully incorporating family spillover effects in pediatric CUAs as part of the societal perspective analysis. Guidelines on methods for incorporating family spillover effects, drawing on best practice where available, are needed. HTA agencies around the world, in their current guidelines, explicitly recommends incorporating only caregiver time costs in the reference case analysis from a societal perspective. This could be expanded to include family

health spillover effects. For instance, the Second Panel on CEA recommends the inclusion of an impact inventory, which is a checklist of health and non-health outcomes and costs to be considered in CEAs (Neumann et al., 2016). This checklist helps know various methodologic elements and inputs the researchers or analysts employed when conducting a CEA. Adding a category for caregivers and family health spillover effects under a societal perspective would be the starting point and encourage researchers to include caregivers and family health spillover effects. If caregivers and family health spillover effects are excluded, analysts could briefly describe rationale in the "Notes on Sources of Evidence" section.

A child's health has both positive and negative impacts on the family's welfare. The type and magnitude of the impacts can be explained by the nature and severity of diseases or conditions, which, in some cases, can cause significant financial and health and wellbeing consequences for family members (Lamsal, chapter 1). It might not be feasible or desirable for all pediatric CUAs to include family health spillover effects in pediatric CUAs. Therefore, the first step would be to identify criteria for inclusion, such as the type of pediatric conditions or diseases that significantly impact family members' health and wellbeing and/or economic wellbeing. A greater understanding of which family members are greatly affected by a child's conditions or illness is likely to be a helpful second step to decide whose spillover effects should be included in pediatric CUAs. The decision to include the family health spillover effects must depend on clinical evidence and clearly justify and report their choices. The next step would be, making it an explicit requirement to incorporate the family spillover effects in the analysis for those pediatric conditions and diseases. This may also encourage researchers or analysts to include family health spillovers in pediatric CUAs and potentially lead to rigorous and standardized methods of measurement, valuation, and incorporation of family health spillover effects in pediatric CUAs.

2.6 Limitations

A limitation of this review is the potential for relevant articles to be missed during the screening process. Some of the pediatric and maternal-perinatal CUAs included in this review did not explicitly state that they had considered the family health spillover effects in texts. For instance,

for one pediatric CUA, we recognized that researchers had considered the family health spillover effects by looking into the tables' footnotes of that study. So, it is likely that researchers might have missed some pediatric and maternal-perinatal CUAs that have included family health spillover effects in the selection process. Second, this review was limited by the information authors have provided in the published pediatric and maternal-perinatal CUAs in this review. For instance, a maternal-perinatal CUA might state that disutilities associated with the disease for neonates and pregnant were estimated separately, and the QALYs were calculated using the life expectancies of pregnant women and children. Furthermore, they might report the combined QALYs gains or losses for pregnant women and children, but they wouldn't say how combined QALYs were estimated. The third limitation of this review is that the primary aim of this review was to review methods used by pediatric CUAs to incorporate the family health spillover effects. However, during the selection process, the researchers noticed many maternal-perinatal CUAs. Integrating the health outcomes of the child and the family member (particularly the mother) is relevant in maternal-perinatal CUAs. Therefore, the researchers decided to include maternal-perinatal CUAs in this review. Although the search strategy was modified to cover maternal-perinatal CUAs, there is a possibility that this review has missed some maternal-perinatal CUAs that have considered the health outcomes of pregnant women and the child. The fourth limitation is that only a single reviewer conducted abstracts and full-texts screening, data extraction and quality assessment. Having more than one reviewer eliminates biases and errors in identifying relevant studies, data extraction, quality assessment and analysis. Lastly, the requirement for studies to be published in the English language and a peer-reviewed journal will have resulted in some studies being excluded.

2.7 Conclusion

Relatively few pediatric CUAs have considered the family health spillovers, and maternal-perinatal CUAs have included the health outcomes of mother and children in analysis. Within those included family health spillover effects and the health outcomes of mothers and children, considerable heterogeneity was observed in methods applied to measure the health outcomes of family members and caregivers and incorporate them into analyses. This illustrates no consensus among researchers on how family health spillover on family members or caregivers should be

measured and valued for cost-utility studies. This review provided a review of methodologies used by both pediatric CUAs and maternal-perinatal CUAs to integrate the health outcome(s) of individuals, family member (s) and caregivers(s), other than a patient in analysis. Further research should explore potential theoretical and practical guidelines incorporating the family health spillover effects in pediatric CUAs. HTA agencies around the world, in their future guideline updates, must have an explicit requirement for the inclusion of family health spillover effects in pediatric CUAs and both maternal and child health outcomes in maternal-perinatal CUAs. This requirement may encourage researchers to include the health outcomes of other family members other than a patient and eventually lead to rigorous and standardized methods for measurement, valuation, and incorporation.

Figure 2-1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses

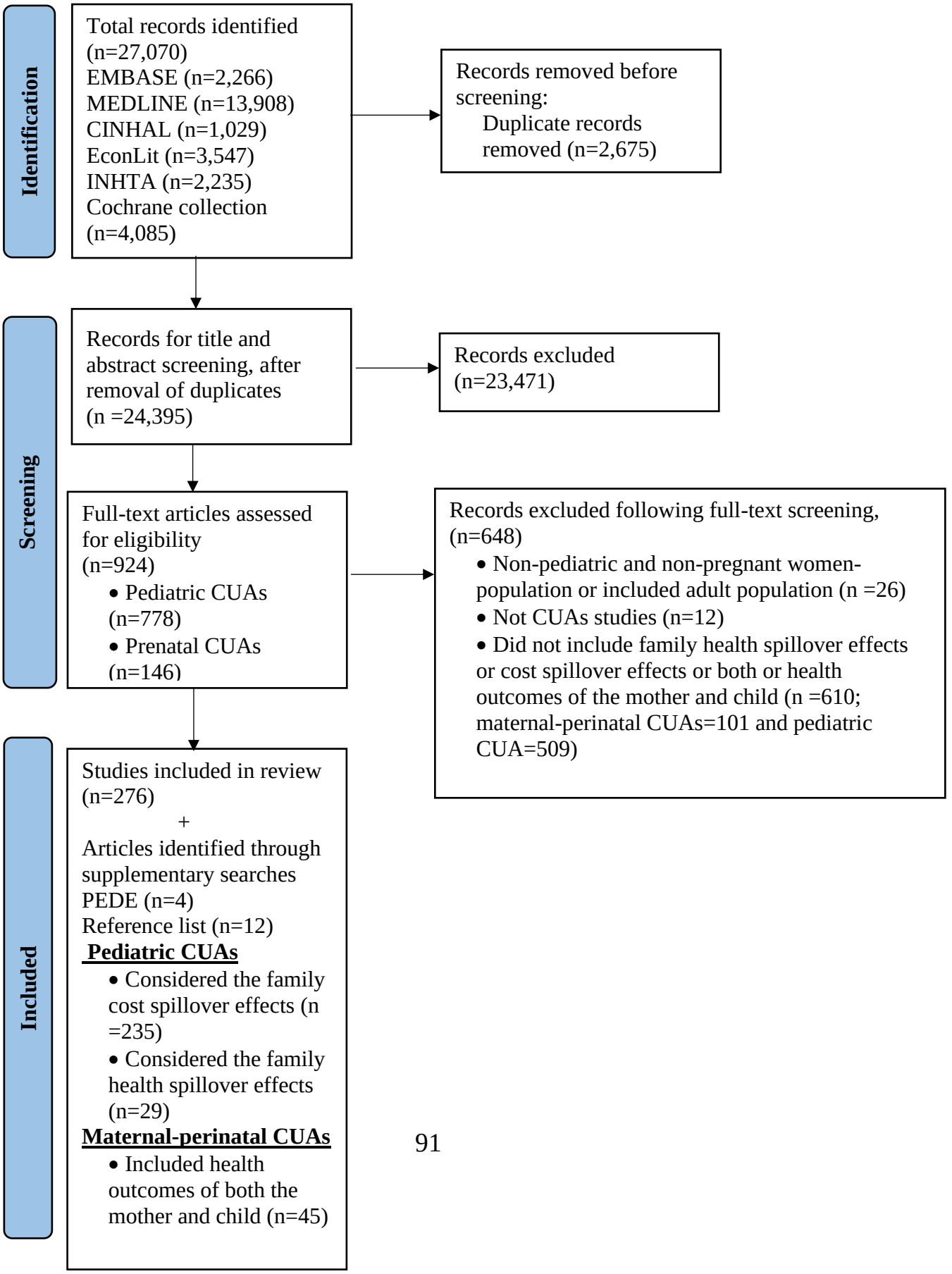


Table 2-1 Summary of Characteristics of Pediatric Cost-utility Analyses Including Family Health Spillover Effects

	n	Percentage (%)
Overall	29	
Publication year		
2000-2005	1	3
2006-2010	8	28
2011-2015	13	45
2016-2020	7	24
Disease or Condition (ICD-11)		
Infectious or parasitic diseases	15	52
Mental, behavioural, or neurodevelopmental disorders	5	17
Endocrine, nutritional or metabolic disorders	2	7
Disease of the nervous system	2	7
Disease of the ear or mastoid process	2	7
Disease of musculoskeletal system or connective tissue	1	3
Disease of the immune system	1	3
Certain conditions originating in the perinatal period	1	3
Intervention type		
Immunization	17	59
Drugs and medications	5	17
Behaviour therapy	2	7
Other	5	17
Country of population		
UK	9	31
USA	5	17
Canada	2	7
Netherlands	2	7

Belgium	2	7
Other	9	31
Age(s) of target population included in study[a]		
Neonate (newborn to 1 month)	8	28
Infant (1 month to 12 months)	12	41
Child (1 to 12 years)	18	62
Adolescent (13 to 18 years)	7	24
Perspective		
Societal and healthcare system	12	41
Societal	7	24
Healthcare system	7	24
Mother and neonatal	1	3
Not stated	2	7

[a]Not mutually exclusive

Table 2-2 Summary of Characteristics of Maternal-perinatal Cost-utility Analyses Including Health Outcomes of the Mother and Child

	n	Percentage (%)
Overall	45	
Publication year		
2000-2005	8	18
2006-2010	7	16
2011-2015	12	27
2016-2020	17	38
2021	1	2
Disease or Condition (ICD-11)		
Maternal infectious and parasitic disease or fetus and newborn affected by maternal infectious and parasitic disease	18	40
Delivery	6	13
Diabetes mellitus in pregnancy	6	13
Maternal and neonatal death	3	7
Congenital maternal heart disease affecting fetus or newborn	2	4
Disease of the circulatory system	1	2
Disease of appendix	1	2
Labor and delivery by vasa Previa	1	2
Maternal care for known or suspected abnormality of pelvic organs	1	2
Maternal care for suspected macrosomia	1	2
Postpartum hemorrhage	1	2
Fetus or newborn affected by maternal use of tobacco	1	2
Other	3	7
Intervention type		
Diagnostic or screening	14	31

Childbirth delivery method	6	13
Other	25	56
Country of population		
USA	24	53
UK	4	9
Uganda	3	7
Other	14	31
Target population included in study[a]		
Pregnant women	12	27
Pregnant women and perinates	7	16
Pregnant women and neonates	6	13
Neonates	5	11
Fetuses	4	9
Perinates	2	4
Infants	2	4
Pregnant women, neonates and infants	2	4
Pregnant women and fetuses	2	4
Pregnant women and children	1	2
Neonates and infants	1	2
Sexually active women	1	2
Perspective		
Societal	19	42
Healthcare system	16	36
Mother and neonatal	3	7
Not stated	7	16

Fetus: an unborn offspring, from the embryo stage until birth; neonates: newborns until the first month of age; perinates: antenatal period up to seven days; infants: one month to one year of age; [a]Not mutually exclusive

Table 2-3 Summary of Quality of Pediatric Cost-utility Analyses

Items	Questions	Yes		No	
		n	Percentage	n	Percentage
1	Was the study objective presented in a clear, specific, and measurable manner?	24	100	0	0
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	23	96	1	4
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	18	75	6	25
4	If estimates came from a subgroup analysis, were the groups pre specified at the beginning of the study?	24	100	0	0
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	22	92	2	8
6	Was incremental analysis performed between alternatives for resources and costs?	24	100	0	0
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	23	96	1	4
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	14	58	10	42
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	21	88	3	12
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they6include the major short-term was justification given for the measures/scales used?	24	100	0	0
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	20	83	4	17
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	24	100	0	0

13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	23	96	1	4
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	1	4	23	96
15	Were the conclusions/recommendations of the study justified and based on the study results?	24	100	0	0
16	Was there a statement disclosing the source of funding for the study?	19	79	5	21

Table 2-4 Summary of the Quality of Maternal-perinatal Cost-utility Analyses

Items	Questions	Yes		No	
		n	Percentage	n	Percentage
1	Was the study objective presented in a clear, specific, and measurable manner?	45	100	0	0
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	36	80	9	20
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	30	67	15	33
4	If estimates came from a subgroup analysis, were the groups pre specified at the beginning of the study?	45	100	0	0
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	41	91	4	9
6	Was incremental analysis performed between alternatives for resources and costs?	44	98	1	2
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	45	100	0	0
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefit sand costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	37	82	8	18
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	34	76	11	24
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they6include the major short-term was justification given for the measures/scales used?	45	100	0	0
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	34	76	11	24

12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	44	98	1	2
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	35	78	10	22
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	0	0	45	100
15	Were the conclusions/recommendations of the study justified and based on the study results?	45	100	0	0
16	Was there a statement disclosing the source of funding for the study?	37	82	8	18

Table 2-5 Summary of Methods for Inclusion of Family Health Spillover Effects in Pediatric Cost-utility Analyses

	Included family health spillover effects (n=29)
Variable	n (%)
Type of family health spillover effects measured	
An inherent approach	9 (31%%)
• Health utility of the caregiver (s)	7 (7%)
• Health utility of the caregiver-child dyad*	1 (13%)
• Other (mapping GHQ-12 to EQ-5D)	1 (3%)
An isolated approach	20 (70%)
• QALY loss of the caregiver due to a child's illness or disability (s)	10 (50%)
• Disutility of a child's illness or disability on the caregiver(s)	5 (25%)
• QALY loss of the caregiver-child dyad**	3 (15%)
• QALY loss of the family due to patient premature death	1 (5%)
• QALY loss of family and network members due to a child's illness or disability	1 (5%)
Modelling Approach	
• Decision analytic model	14 (48%)
• One decision analytic model	13 (92%)
• Two decision analytic models	1 (8%)
• Statistical model	14 (48%)
• Not clear	1 (4%)
Integration of family health spillover effects	
Inclusion in the reference case analysis	19 (65%)
• Estimated health utilities separately for caregivers and children and the mean total QALY losses or gains due to the treatment for caregivers and children calculated and reported separately	3 (16%)
• Estimated the mean total QALY losses for caregivers and children separately and the mean total QALY losses caregivers and children were summed, and a combined mean total QALY gains or losses for caregivers and children due to the treatment calculated and reported.	3 (16%)

• Estimated heath utilities separately for caregivers and children, and the mean total QALY gains or losses for caregivers and children due to the treatment calculated separately, and then total QALY gains or losses for children and caregivers due to the treatment summed. A combined and separate the mean total QALY gains or losses due to the treatment for caregivers (parents) and children reported	3 (16%)
• Estimated mean total QALY losses for caregivers and children separately, and then the mean total QALY losses for caregivers and children were summed. A combined and separate mean total QALY gains or losses for caregiver and children due to the treatment reported.	3 (16%)
• Disutilities of a child's illness or disability on the caregiver(s) were subtracted from the child health utility and the mean total QALY gains, or losses estimated and reported only for children	2 (10%)
• Estimated QALY loss for caregiver-child dyad and subtracted from respective child health state and then, a combined the mean total QALY gains or losses for caregivers and children calculated and reported	2 (10%)
• Estimated QALY loss for caregiver-child dyad and a combined mean total QALY gains or losses for caregivers and children calculated using time-trade off method. A combined mean total QALY gains or losses for caregivers due to the treatment children reported	1 (5%)
• Estimated health utilities for caregiver-child dyad and a combined mean total QALY gains, or losses due to the treatment calculated and reported	1 (5%)
Inclusion in sensitivity or scenario analysis	10 (35%)
• Total QALY losses were summed with the child QALY losses	6 (60%)
• Disutility or utility decrements subtracted from the child health utility	4 (40%)

QALY, quality-adjusted life-year

*The caregiver-child dyad health utility represents the combined current health states of both the caregiver and the child

** The caregiver-child dyad lost represent pains and suffering of the child and caregiver from the child's disease in single number

Table 2-6 Summary of Methods for Integration of Mother and Child Health Outcomes in Maternal-perinatal Cost-utility Analyses

	Included health outcomes of pregnant women and fetuses, neonates, perinates and infants* (n=45)
Variable	**n (%)**
Type of health outcomes measured	
QALY based maternal-perinatal CUAs	35 (78%)
• Health utilities of pregnant women and children	22 (62%)
• QALY loss of pregnant women and children due to the disease	3 (8%)
• Disutilites associated with the disease for pregnant women and children	2 (6%)
• Disutilites associated with the disease for pregnant women and children and QALY of pregnant women and children	2 (6%)
• QALY of pregnant women and children	1 (3%)
• QALY loss of pregnant women and children due to the disease and QALY of pregnant women and children	1 (3%)
• QALY loss of pregnant women and children due to the disease and disutilites associated with the disease for pregnant women and children	1 (3%)
• Health utilities of children and disutilities associated with disease for pregnant women	1 (3%)
• QALY of pregnant women-child dyad	1 (3%)
• Health utilities of pregnant women-child dyad	1 (3%)
DALY based maternal-perinatal CUAs	10 (22%)
• DALY averted of pregnant women and children	10 (100%)
Modelling Approach	
• Decision analytic model	42 (93%)
• One decision analytic model	40 (95%)

• Two decision analytic models	2 (5%)
• Statistical model	2 (5%)
• Not clear	1 (2%)
Integration of the health outcomes of pregnant women and Fetuses, Neonates, Perinates and Infants	
QALY based maternal-perinatal CUAs	35(78%)
• Estimated health utilities separately for pregnant women and children, and the mean total QALY for pregnant women and children due to the treatment were summed. A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported.	17 (48%)
• Estimated the mean QALY losses for pregnant women and children separately, and then the mean total QALY losses for pregnant women and children were summed. A combined mean total QALY gains or losses for mothers and children due to the treatment reported.	4 (11%)
• Estimated utilities separately for pregnant women and children, and the mean total QALYs were estimated separately for pregnant women and children. The mean total QALY gains or losses due to the treatment were reported separately for pregnant women and children	3 (8%)
• Estimated disutilities associated with the disease for pregnant women and children, and the mean total QALYs for pregnant women and children were summed. A combined total QALY losses or gains due to the treatment for pregnant women and children calculated and reported	2 (6%)
• Estimated the mean total QALY and disutilites associated with the disease separately for pregnant women and children and, the mean total QALY losses or gains due to the treatment were calculated separately for pregnant women and children	2 (6%)
• Estimated total pregnant -women-child dyad QALY and a combined mean total QALY gains or losses for pregnant women and children due to the treatment was calculated and reported	1 (3%)
• Estimated health utilities of pregnant women-child dyad and a combined mean total QALY gains or losses due to the treatment for pregnant women and children calculated and reported	1 (3%)

• Estimated the mean total QALY and QALY losses for pregnant women and children separately, and then mean total QALY for pregnant women and children were summed. A combined mean total QALY gains or losses for pregnant women and children due to the treatment was reported.	1 (3%)
• Estimated the mean QALY loss and disutilites associated with the disease were separately for pregnant women and children, the mean total QALYs loss were summed. A total combined mean QALY gains or losses for children and pregnant women due to the treatment was reported	1 (3%)
• Estimated health utilities and disutilities associated with the disease separately for pregnant women and children and the mean total QALYs for pregnant women and children were summed. A combined mean QALY gains or losses due to smoking cessation intervention for pregnant women and children was reported	1(3%)
• Estimated health utilities separately for pregnant women and children and the mean total QALY for pregnant women and children were summed. A combined and separate mean total QALY gains or losses due to the treatment for pregnant women and children reported	1 (3%)
• Estimated health utilities separately for pregnant women and children and the mean total QALY were estimated and reported separately for pregnant women and children	1 (3%)
DALY based maternal-perinatal CUAs	10 (35%)
• Estimated total DALYs averted by intervention or treatment for pregnant women and children separately and then, total DALYs averted by intervention or treatment for pregnant women and children were summed. A combined and/or separate mean total DALYs averted by intervention or treatment for pregnant women and children reported.	10 (100%)

QALY, quality-adjusted life-year; DALY, disability-adjusted life year

Fetus: an unborn offspring, from the embryo stage until birth; neonates: newborns until the first month of age; perinates: antenatal period up to seven days; infants: one month to one year of age. Fetuses, neonates, perinates and infants are referred as children for reporting/ summarising. The details can be found in table 4.

3 A theoretical Framework for Conducting Pediatric Economic Evaluation from a Family Perspective

3.1 Introduction

Economists have long recognized that the costs and benefits of health treatments or programs can accrue to non-targeted recipients (Culyer & Simpson, 1980; Jones-Lee, 1992; Labelle & Hurley, 1992; Russell, 1999). Yet, the current approach in adult or pediatric economic evaluation treats patients as isolated individuals, ignoring the potential effects (positive and negative) of their illness on family members. In our recent review of pediatric cost-utility analyses (CUA) for the inclusion of effects on family members, we found that out of 778, only 29 pediatric CUAs had included health outcomes, and 253 pediatric CUA had included the costs of caregivers or parents or family (Chapter, 2). Importantly, however, it would be uncommon to identify a scenario where a child's health condition does not significantly impact the welfare of all family members. For example, meeting the high care demands and diverse needs of services for children with chronic illness or disability imposes psychological distress, depression, anxiety, and other mental health problems on family members (Cohn et al., 2020; M. H. Lee et al., 2017; Martin Pinquart & Sörensen, 2003). Families may experience financial hardships because of lost income and high healthcare expenses, including out-of-pocket costs for treatments for the child's health and the costs of caregivers' own health service use for health problems caused by caregiving physical and mental strain (Anderson et al., 2007a; Brouwer, 2006; Stabile & Allin, 2012; Tsimicalis et al., 2011). Such effects are commonly described as 'spillover effects,' 'spillovers,' and 'externalities' within the health economic literature (Basu & Metlzer, 2005; Labelle & Hurley, 1992; Muir & Keim-Malpass, 2020). This chapter is focused on the family spillover effects -- the impacts of a child's disability or illness on family members. It can be categorized into 'family cost spillover effects.' i.e., monetary effects such as productivity costs and out-of-pocket costs, and 'family health spillover effects' -- non-monetary effects such as health and well-being effects. The family health spillover effects stem from family effects and caregiver/caregiving effects. Family effects occur in family members occur due to witnessing the suffering or worse health state of a loved one, a child, '*caring about other*' (Bobinac, Van Exel, et al., 2010, 2011;

Brouwer, 2019) Caregiver effects occur in parents due to proving care for a child with chronic illness or disability, *caring for other*' (Bobinac, van Exel, et al., 2011; Brouwer, 2019). Family effects and caregiver effects are discussed in detail in chapters 1 and 2. While both family health and cost spillover effects represent family spillover effects on family members, family cost spillover effects, particularly productivity costs of parent(s) due to caregiving and out-of-pocket costs or co-payments of parent(s) for medical and/or non-medical services for the child (e.g., co-payments for drugs or special equipment for the child with chronic illness or disability) are frequently considered for inclusion in the pediatric economic evaluation (Lavelle et al., 2018).

Consequently, it is evident that implementing any intervention/treatment or changes in care to improve the health and well-being of a chronically ill child could have health and well-being-related effects and cost consequences for family members. For instance, interventions aimed at reducing autism spectrum disorder (ASD) symptoms in children may also improve their family members' quality of life (QoL) by releasing them from emotionally and physically demanding caring responsibilities (Estes, Swain, & MacDuffie, 2019). As a result, parents might be able to return to work earlier or seek employment. On the other hand, interventions that improve health in children with a chronic illness may prevent children from being admitted to the hospital and result in additional caregiving responsibilities for parents. Subsequently, parents may need to quit a job or reduce working hours to care for a child. Yet, parents may feel happier because their child's health is better and/or because their children are at home, and they are participating directly in the child's care. Furthermore, parents (caregivers) may experience positive effects through the feelings of being appreciated by the cared-for patient (the child) and other family members (Davidson and Levin, 2010). Al-Janabi and colleagues, in their qualitative study of caring experience for adult patients, interviewed 16 caregivers who were caring or had recently cared for someone who is over 65. Caregivers had positive feelings from caregiving, including being appreciated by the care receiver, making someone happy, and contributing to the care of a loved one. A male caregiver of a wife with mental health problems stated '…sometimes she'll look up to me and give me such a priceless lovely smile, which says it all and then the other morning she laid down for a bit and looked up to me and said, "you're lovely, I love you." It came out as clear as a bell. Well, you can't put a price on that, can you?'.

In an effort to provide a theoretical framework for the inclusion of externalities, Labelle and Hurley devised the concept of "societal utility," whose theoretical underpinning is derived from welfare economics (Labelle & Hurley, 1992). The societal utility is the function of patient utility from treatment and associated utilities from three types of externality: (1) non-patient utility derived from the treatment of patients, i.e. one person's consumption of health care affects another person's utility, (2) patient utility derived from the treatment of other patients, which refers to the utility that a patient derives from the knowledge that other patients with the same condition are receiving treatment and (3) non-patient utility derived from option value, where an individual derived the utility from having the option to utilize the health care services in the future, even though some individuals may never actually use the health care services.

In subsequent work, Basu and Meltzer adopted a welfarist approach to propose a theoretical framework for the inclusion of spillover effects into CUA from a societal perspective (Basu & Metlzer, 2005). Based on a family utility function model with altruistic linkage, the authors assumed that "there is some level of caring or altruism present in the family and that family members jointly make decisions that are efficient." An individual derives utility not only from his/her consumption and health but also from the consumption and health of his/her family members. In this collective family approach, the treatment choice (e.g., purchasing medical care) for a patient within a two-person household consisting of a husband and a wife is influenced by the expected direct benefits from treatment to the patient and the associated expected benefits to the spouse from the patient's treatment, and the indirect benefits to the patient through his/her spouse from the patient's treatment. The total effect of a patient's disease-related health state from a societal perspective is the sum of the direct effects of disease on the patient's utility and total spillover effects within the family (indirect effect on the patient's utility of family member's utility + direct effect of patient's disease on family members' utility).

Nevertheless, others have argued that the health spillover effects in economic evaluations should be defined more broadly instead of (health) utility per se. Al-Janabi et al. developed a conceptual framework for including family spillover effects based on the extra-welfarist approach (Al-Janabi et al., 2016). Unlike the Basu and Meltzer, and Labelle and Hurley theoretical frameworks based on the welfare approach where the focus is on maximizing the utility of the family or the

society, Al-Janabi et al.'s framework focus on maximizing the health benefits to the population from a fixed healthcare budget. Al-Janabi et al.'s framework incorporate health spillover effects into the conventional economic evaluation by including two multiplier effects (Al-Janabi et al., 2016). One multiplier refers to the health benefits of providing a new intervention for patients and their family networks. Another for the health displaced of patients and their family networks by funding this intervention. These multiplier effects represent the ratio of incremental total health benefits (comprising health benefits to patients and their family members) to incremental patient health benefits from the intervention.

Literature has alluded to causes of omission of family spillover effects, particularly family health spillover effects, on family members in economic evaluations, including pediatric economic evaluations. These include the lack of established theoretical frameworks for the inclusion of family spillover effects and the lack of methods for measuring and valuing changes in family health spillover effects (Brouwer, van Exel, Koopmanschap, & Rutten, 1999; Prosser & Wittenberg, 2019b; J. M. Tilford & N. Payakachat, 2015; Ungar, 2011). Chapter 2 revealed that researchers or analysts have used various methods or approaches to integrate the health spillover effects in pediatric CUAs. However, few researchers used theories and/or theoretical frameworks or provided justifications for the methods used to incorporate health spillover effects in caregivers and/or parents.

Considerable progress has been made in measuring and valuing the family cost and health spillover effects; however, much work is warranted in developing theoretical and empirical methods to incorporate family spillover effects in economic evaluations. Despite the potential usefulness of the abovementioned theoretical frameworks in economic evaluation in general, these theoretical frameworks are developed in the context of adult economic evaluations. There is a significant difference between child and adult health that needs to be acknowledged while considering the family spillover effects for pediatric health economic evaluation. These differences between child and adult health can be categorized into three broad categories: development, interdependency, and patterns of resource use (Keren et al., 2004; Prosser, 2009; Ungar & Gerber, 2010).

A child's development and subsequent transformation into adulthood are the product of several factors at the individual, family, and community levels (R. Q. Bell, 1968; Bronfenbrenner, 1986; Piaget & Cook, 1952; A. Sameroff, 1975; Ungar & Gerber, 2010). This transformation is manifested by a series of physical, emotional, behavioural, cognitive, and social changes. More importantly, a child's health and development are intertwined with their parents' health and other family members' health and well-being. This bidirectional relationship has been demonstrated by several empirical studies on the parent-child relationship, in which children and parents have been observed to influence each other's health and well-being (Bakula et al., 2019; C. M. Bell, Araki, & Neumann, 2001; J. Lee, 2013; Scherer et al., 2019). Second, children are dependent on their parents and other family members. Starting with comprehensive care at the beginning of life to meet basic needs, it will take the next two decades for children to become gradually more independent. Parents are the decision-makers for a child for his or her health care needs. The dependency is even more pronounced for children with disabilities or chronic illness and extends to adulthood because of cognitive, communication and physical limitations associated with illness or disabilities (Amato et al., 2014; Kennes et al., 2002; Mâsse et al., 2013). It is evident that this waning yet prolonged period of dependency impacts parents' or family members' health and well-being on whom the children depend. Finally, as mentioned above, parents invest in healthcare resource consumption because children cannot independently decide about investment in their own health. Parents' decisions regarding healthcare resource consumption for a child depend on family socioeconomic status, the need to spend on the health and well-being of the other family members, including parents and siblings, a family's cultural values and beliefs, available resources, and parental altruism toward children (Anderson et al., 2007a; Apps & Rees, 2001; Becker, 1981; L. Jacobson, 2000). Furthermore, it is essential to acknowledge that the child's development and well-being are embedded in multiple contexts, including their peer group, the classroom, and the community (Bronfenbrenner, 1986; Ungar & Gerber, 2010). Understanding these complex and changing relationships between the child's health and development and their family, friends, and community is essential in creating a theoretical framework for including family spillover effects in pediatric economic evaluation.

For this study, a *theory* is defined as logically related statements that present a systematic view of phenomena or situations described by relationships among concepts (Abend, 2008; Glanz,

Rimer, & Viswanath, 2008; Kerlinger, 1966). A theory explains how and why the specific relationships between concepts lead to phenomena or situations and predict what might happen in the future (Carpiano & Daley, 2006; Kivunja, 2018). A theory is an abstract description of the relationships between concepts that helps to understand the world (Abend, 2008; Kerlinger, 1966; Kivunja, 2018). A theory is testable—the more evidence supports it, the stronger it becomes (Abend, 2008; Carpiano & Daley, 2006). A theoretical framework is a logically related set of concepts or premises developed from one or more theories and/or previously tested and published knowledge (Abend, 2008; Kerlinger, 1966). The theoretical framework summaries *theories and/or ideas*. It directs the analytic approach that supports the research questions (Kivunja, 2018; Varpio, Paradis, Uijtdehaage, & Young, 2020). For instance, theoretical frameworks help researchers answer what existing theories or ideas researchers can use to investigate and understand the research problem? In the objectivist deductive approach (theory to data), researchers typically create the theoretical framework before the data collection and is fixed throughout the research (Kivunja, 2018; Sabatier, 2019). In the subjectivist inductive approach, researchers propose a tentative theoretical framework before the study is carried out, then refine it as data are collected and the researcher's understanding of the problems evolves (Kivunja, 2018). A conceptual framework identifies a set of the key factors, constructs, or variables and their relations and integrates them to describe a phenomenon (Kivunja, 2018; Varpio et al., 2020). The conceptual framework describes the state of general knowledge, identifies gaps in understanding a problem and may outline the methodological underpinnings of the proposed research project (Sabatier, 1991, 2019; Varpio et al., 2020). The researcher develops the conceptual framework through a literature review and does not need to be existing theories (Carpiano & Daley, 2006; Sabatier, 1991). Finally, a model is narrower in focus than theory and theoretical framework. A model is developed within a theoretical and/or framework and attempts to describe and simplify the specific and/or aspect of a phenomenon or concept (Carpiano & Daley, 2006). A model may also draw upon several theories or theoretical frameworks to explore a particular phenomenon in a specific setting (Carpiano & Daley, 2006). Models make particular assumptions about how a limited set of variables are interrelated (Carpiano & Daley, 2006; Ostrom, 2019). These assumptions are systematically explored and tested on a limited set of outcomes by a specific method(s) (Carpiano & Daley, 2006; Kivunja,

2018; Varpio et al., 2020). Variables in the model can be measured and controlled for experimentation (Carpiano & Daley, 2006; Kivunja, 2018; Weber, 2017). Variables are the empirical counterparts or operational forms of concepts (Carpiano & Daley, 2006; Kivunja, 2018).

This chapter aimed to 1) critically review existing theories, conceptual frameworks, and models that support the consideration of family spillover effects in pediatric economic evaluation or emphasize using a family (or household) level approach in providing care for the child or understanding the child's health and development, 2)synthesize and integrate information into a comprehensive theoretical framework for incorporating family health and cost spillover effects in pediatric economic evaluation, and 3) propose an approach for incorporating family health and cost spillover effects in the pediatric cost-utility analysis based on the proposed theoretical framework.

3.2 Methods

A scoping review was conducted using the methodological framework developed by Arksey and O' Malley and further enhanced by Levac and colleagues (Arksey & O'Malley, 2005; Levac, Colquhoun, & O'Brien, 2010). This review included five stages: 1) identifying the research question, 2) defining the search strategy, 3) study selection, 4) charting data, and 5) collating, summarizing, and reporting results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews was used to report the results (Tricco et al., 2018). Critical Interpretive Synthesis (CIS) principles were used to guide data analysis and integrate evidence from studies from diverse disciplines into a comprehensible theoretical framework for the inclusion of family spillover effects in pediatric economic evaluation (Mary Dixon-Woods et al., 2006). CIS is based on the conventional review process yet allows incorporating insights and interpretation drawn from selected empirical and non-empirical literature. CIS uses an inductive approach to the data analysis, and the process is iterative. In addition to data aggregation and data synthesis (i.e., identifying those findings that recurred most frequently across the included studies), CIS enables identifying new constructs grounded in included studies and synthesizing arguments to create a theoretical framework that cannot be done through the use of conventional systematic or scoping reviews (M. Dixon-Woods, Agarwal,

Jones, Young, & Sutton, 2005; Mary Dixon-Woods et al., 2006; Wilson et al., 2014). The inductive analysis involves detailed readings of raw qualitative data to derive concepts or themes interpretations made from the raw qualitative data by the researcher (D. R. Thomas, 2003, 2006). Qualitative data is non-numerical data, such as text, video, photographs, or audio recordings. This type of data can be collected using diary accounts, in-depth interviews, or previously published studies. This approach is best suited for developing theoretical frameworks that draw on evidence from heterogeneous sources and is particularly useful when a distinct body of literature is not clearly defined (Boyko, Lavis, Abelson, Dobbins, & Carter, 2012; Mary Dixon-Woods et al., 2006; Wilson et al., 2014). The objectives of this review, mentioned below, fit well with the core objective of the CIS approach.

3.2.1 Identifying the Research Question

The research question that guided this study was: 'What theories, conceptual frameworks and models support the reasons why family health or cost spillover effects or both should be considered in pediatric economic evaluation?' The objectives of this review were to:

1. Identify and synthesize relevant theories, conceptual frameworks, and models relevant to the following three topics:
   1.1. consideration of family spillover effects to understand the child's development and health.
   1.2. use of a family or household level approach to provide care for the child.
   1.3. using a family or household level approach to understand child development and health.
2. Building on the preceding objective, to develop a theoretical framework for incorporating family health and cost spillover effects in pediatric economic evaluation.

   2.1. based on the proposed theoretical framework, to develop an approach for incorporating family health and cost spillover effects in the pediatric cost-utility analysis, a particular type of economic evaluation.

3.2.2 Defining the Search Strategy and Study Selection

A table of Boolean-linked Medical Subject Headings (MeSH) and text words was constructed using concepts encompassed in the research question, the researcher's prior knowledge of the

topic and search strategies used by related published literature reviews (Booth & Carroll, 2015; Lavelle et al., 2018). After several iterations, a comprehensive search was undertaken in MEDLINE by a single reviewer (RL), followed by the analysis of texts in titles, abstracts, and keywords used to describe key studies. An academic librarian at the University of Toronto was consulted to validate included databases and search strategies. The librarian reviewed the draft of the MEDLINE version of the search strategy. Minor adjustments were made to increase the sensitivity and specificity of the search strategy. Search strategies for the remaining databases were created based on a search string developed for MEDLINE. Between 15 September 2020 and 30 September 2020, the following databases were searched: MEDLINE, Embase, CINAHL, Psych Info, Scopus, EconLit and Sociological Abstracts. All databases were searched from the date of inception of the database. The search strategy comprises a combination of terms describing theories, conceptual frameworks, and models; children; and spillover effects and household effects. The final search strategies for databases, including MEDLINE, can be found in Appendix B. Duplicates of identified articles were removed using EndNote X8.2.

A pre-defined explicit set of inclusion and exclusion criteria were created to identify relevant studies. Inclusion and exclusion criteria were applied in two stages. First, a single author (RL) reviewed the titles and abstracts of retrieved records. Retrieved records were retained during stage one if a review of the title and abstract indicated that the study presents a theory, conceptual framework or model on child health or child development or family health (if theories, conceptual frameworks, or models are on family health, they must include child health). Abstracts, theses or dissertations, reports, and case studies were excluded in the first stage. The peer-reviewed publications and book chapters were eligible for the second stage of screening. The requirement for studies to be published in the English language was also incorporated in the first stage. Full texts of papers remaining after stage one were retrieved for closer inspection in stage two. The second stage involved the hierarchical application of the exclusion criteria. First, studies were excluded if they did not mention a theory, a conceptual framework, or a model. Also, non-theoretical studies or technical papers on child health and development or family health were excluded. Second, studies were excluded if a theory, a conceptual framework, or a model mentioned and described were not designed to understand the child's (≤18y) health and development. These included studies presenting a theory, or a conceptual framework or a model

on family health or household health but did not explicitly include a child. For instance, Basu and Meltzer's theoretical framework on the inclusion of family spillover effects was excluded because it was designed for a two-person household (husband and wife) and did not include a child (Basu & Metlzer, 2005). Third, papers illustrating theory application or theory extension studies and papers making a claim or argument based on existing theories and supported by empirical evidence were excluded. However, studies that were an extension of the original theory that involved extending the theory or assumptions underlying the original theory to include new concepts identified by an author(s) were included in this review. For instance, Jacobson (L. Jacobson, 2000) extended the Grossman health capital model (Grossman, 1972) to incorporate the family perspective and was eligible. Finally, studies were excluded (i) if a theory or a conceptual framework, or a model mentioned and described does not support consideration of family cost spillover effects or family health spillover effects or both, (ii) do not emphasize using a family or household level approach in providing care for the child and (iii) do not emphasize using the family or household level approach in understanding the child health and development. A single reviewer (RL) manually searched for additional potentially eligible articles by screening the reference lists of included articles and reviews. If included articles were about the application of a theory, the author then manually searched for the original theoretical articles on the original theory.

3.2.3 Data Extraction

Data extraction was conducted in the following manner. First, each included paper was read several times to understand emerging key concepts related to the child's health and development, its process, and kinships with the family members. Next, a single author independently extracted data using a standardized data collection form developed in Microsoft word. Information extracted included authors, year of publication, name of theories, conceptual frameworks or models, type of theories (original or conceptual frameworks or models) and discipline. The data abstraction form was constantly updated based on emerging information from theories, conceptual frameworks, or models in consultation with other authors. Furthermore, the context in which a theory, a conceptual framework or model was presented and a summary of a theory, a conceptual framework or model were extracted. Second, a single author extracted the major

concepts (verbatim statements) from each included theory, conceptual framework, or model. Attention was given to answer the following questions: (1) *Who?* Which family members are involved? (2) *How?* Which aspect of the phenomenon (trend, event, happening) are described, and how has it impacted other family members' health and well-being and financial well-being? 3) *How?* Which aspect of the phenomenon (trend, event, happening) are described, and how has it helped to understand the child's development and health? 4) *Why?* What explanations are described to include family spillover effects in understanding child health and development? 5) *Why?* What explanations are described to use the family level or household level approach in understanding child health and development? Finally, included theories, conceptual frameworks, or models were classified into the following groups: (1) considers family health or cost spillover effects in understanding child health and development, (2) emphasizes using a family or household level approach to understanding child development and health, or (3) emphasizes using a family or household level approach to provide care for the child. These groups are not mutually exclusive.

3.2.4 Quality Appraisal

Assessing the quality of included theories, conceptual frameworks, and models is essential when the review aims to construct a coherent theoretical framework for integrating relevant insights from selected theories, conceptual frameworks, and models. Critical appraisals of the methodological quality of included quantitative and qualitative studies in systematic reviews are very common (Katrak, Bialocerkowski, Massy-Westropp, Kumar, & Grimmer, 2004; Zeng et al., 2015). It enables reviewers to determine the strength of evidence and the potential for bias relating to specific findings (Zeng et al., 2015). The quality of theories, conceptual frameworks, and models cannot be appraised using the kinds of tools that have been developed for quantitative and qualitative studies included in conventional reviews, most of which tend to focus on internal validity and study design. The focus is no longer on the methodological quality but on the quality in which theories, conceptual frameworks, and models are developed, tested, and validated. No standardized and validated critical appraisal tools are developed to access the quality of included theories, conceptual frameworks, and models in constructing a theoretical framework. Therefore, a critical appraisal tool was designed to assess the quality of included

theories, conceptual frameworks, and models. It is important to note here that the goal is to appraise critically theories, conceptual frameworks, and models, not the quality of their applications in research or particular study.

A tool is presented in table 3-1. It includes four items. Questions one to three have four answer categories, 'yes,' 'no,' 'not clear,' and 'not applicable, and question four has answer categories, 'yes,' and 'no.' Each criterion can receive a score of 0 to 1 ('yes'=1 and 'no' or unclear,' and 'not applicable=0). The total scores for the study can range from zero to four (the higher scores indicate the higher quality). The quality assessment of included studies was performed by a single researcher (RL).

3.2.5 Data Analysis and Synthesis

The data analysis and interpretative synthesis were conducted based on the principles of CIS developed by Dixon-Woods et al. (Mary Dixon-Woods et al., 2006), while the coding was done using grounded theory (Glaser & Strauss, 2017; Saldaña, 2021). NVivo software version 12.0 was used to conduct qualitative data analysis. The analyses proceeded in six iterative and sequential phases. The first step was to get familiarized with the data by closely reading each study multiple times (Braun & Clarke, 2006). The second step involved open coding based on the grounded theory, which entailed repeated, in-depth and line-by-line analysis and coding of the major concepts from each included theories, conceptual frameworks and models to identify recurring themes, concepts and ideas (Saldaña, 2021). This process is referred to as reciprocal translation analysis (RTA) in CIS (Mary Dixon-Woods et al., 2006). A single reviewer independently coded all major concepts from included theories, conceptual frameworks, or models. A second reviewer (LR) independently conducted open coding of 31% of randomly selected studies. Both reviewers discussed their codes and discrepancies until consensus was achieved. In the third step, selective coding was carried out by examining the relationship among codes and their contexts and consequences (Strauss & Corbin, 1998). Following the CIS, this involved comparing different synthesized constructs across theories to select the most acceptable one (Mary Dixon-Woods et al., 2006). Both authors jointly grouped these codes into synthesized constructs and added new codes and concepts as they emerged. This process continued iteratively, whereby codes and synthesized constructs were compared systematically

against previously collected data, codes, and synthesized constructs, to find similarities and differences until saturation was reached.

The fourth step involved developing concepts for each synthesized constructs by interpreting the underlying evidence found in theories, conceptual frameworks, and models (Mary Dixon-Woods et al., 2006). *Synthesized (or synthetic) constructs* are theoretical categories built on the explanations and interpretations of the included studies (M. Dixon-Woods et al., 2005; Mary Dixon-Woods et al., 2006). The interpretations of synthesized construct are consistent with the original studies in traditional qualitative inquiry. CIS also allows for developing interpretations that go beyond those offered in the original sources (M. Dixon-Woods et al., 2005; Mary Dixon-Woods et al., 2006). *Concepts* are building blocks of a theory or theoretical framework. The concept can vary in the extent to which they have meaning or can be understood outside the context of a particular theory or theoretical framework (Glanz et al., 2008). Using the constant comparison method, emerging concepts were constantly compared with the data ((major concepts (verbatim statements) of included studies)) at various data abstraction levels to ensure that emerging concepts were grounded in the data extracted from theories, conceptual frameworks, and models (Mary Dixon-Woods et al., 2006; Glaser & Strauss, 2017; Saldaña, 2021; Suddaby, 2006). The emerging concepts were evaluated in the light of the whole evidence of included theories, models, and conceptual frameworks in relation to the research objective and establishing the relationships between emerging concepts (M. Dixon-Woods et al., 2005; Mary Dixon-Woods et al., 2006). In the fifth step, emerging concepts were integrated to create a 'synthesizing argument' as a theoretical framework for incorporating family health and cost spillover effects in the pediatric economic evaluation (Mary Dixon-Woods et al., 2006). Figure 3-1 shows the process of synthesis.

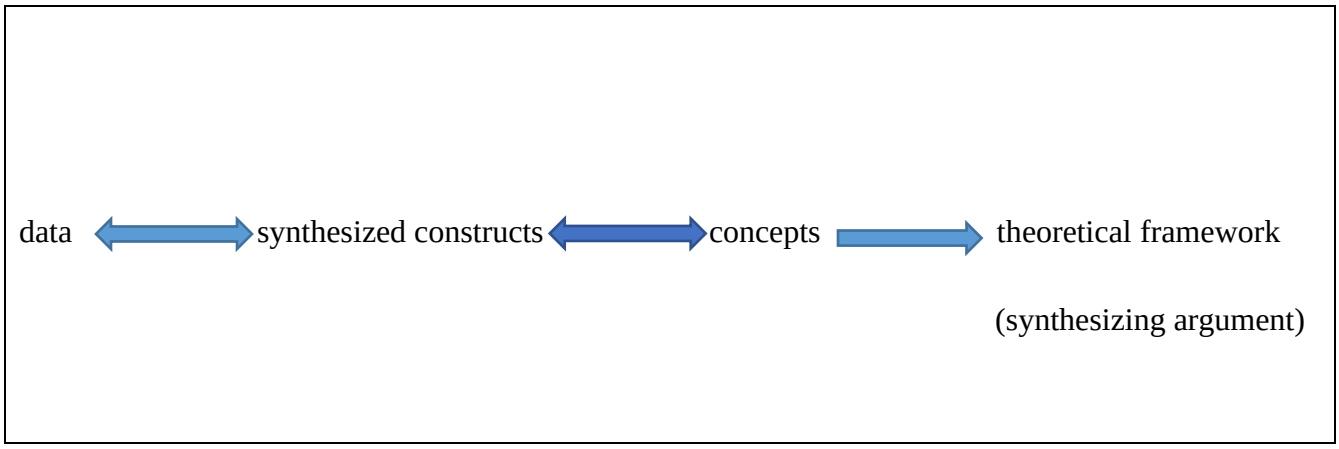


Figure 3-1 Process of Synthesis in the Critical Interpretative Synthesis

Finally, the proposed theoretical framework was reviewed with the second author (LR) by discussing the data analysis and data synthesis at various stages, i.e., the coding process, development of constructs and their integration to form a theoretical framework. The thesis committee members were also involved in various stages of research. The first author regularly met with the thesis committee and incorporated the feedback. The thesis committee provided inclusion and exclusion criteria in the early research process. After consultation with the second author, the first author presented the codes, synthesized constructs, and incorporated feedback. The first author also sought and received input s from thesis committee members on developed concepts and their integration from a theoretical framework. The first author wrote conceptual and theoretical memos throughout the study (Glaser, 1978; Glaser & Strauss, 2017; Saldaña, 2021). These memos were used to record the author's thinking process about the meaning and similarities, and differences between codes and concepts. These memos were constantly updated throughout the data synthesis, for instance, after each discussion with co-authors.

3.3 Results

3.3.1 Search Results

A total of 10,830 unique records were identified from electronic searches, from which 10,675 were excluded based on reading the titles and abstracts (See Figure 3-2). The full texts of the 155 studies were accessed. The first author was unable to find the full texts of four book chapters. Of these 151, 142 were excluded because they did not mention a theory, a conceptual framework, or

a model (n=65), theories, conceptual frameworks or models were not intended for a child (n=26), were theories application studies or theories extensions (n= 38) or did not support consideration of family spillover effects or did not emphasize using a family or household level approach (n=9). An additional three studies were identified through manual searches resulting in 16 total eligible theories, conceptual frameworks, or models. Figure 2 provides a flowchart describing the study selection process and the reasons for exclusion at each screening stage.

3.3.2 Study Characteristics

A summary of study characteristics for the 16 theories or conceptual frameworks or models is provided in Table 3-2. Ten theories or conceptual frameworks or models were original, and the remaining six were applications or extensions of theories. The majority of identified theories or conceptual frameworks or models were from the psychology discipline, followed by health services research, economics, and others. Theories, conceptual frameworks, and models from a broad range of disciplines, as seen in table 1, illustrate the diverse perspectives taken by the authors of these theories or conceptual frameworks or models in understanding the multi-dimensional factors that shape the child's health and development in the family context.

Table 3-3 provides a detailed description of included theories, conceptual frameworks, or models. It contains a short description of each theory or conceptual framework or model, the context in which authors introduced a theory or conceptual framework or model, and the pre-identified group listed in the objectives to which these theories or conceptual frameworks or models belong. Across the 16 theories or conceptual frameworks or models, seven supported considering the family cost and/or health spillover effects in understanding child development and health (Anderson et al., 2007a; Apps & Rees, 2001; Becker, 2009; Bowlby & Ainsworth, 2013; Lynch & Morley, 1995; McConkie-Rosell & Spiridigliozzi, 2004), six emphasized using a family or household approach in providing care for the child (Bowen, 1966; Bowlby & Ainsworth, 2013; P. Christensen, 2004; Golan & Weizman, 2001; Lynch & Morley, 1995; McConkie-Rosell & Spiridigliozzi, 2004), and eight emphasized using a family or household approach in understanding the child health and development (Annett, 2001; Apps & Rees, 2001; Becker, 2009; Berman, Kendall, & Bhattacharyya, 1994; Fosco & Grych, 2013; L. Jacobson, 2000; A. Sameroff, 1975; Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012).

Among the 16 included theories or conceptual frameworks or models, six were on providing care for children with disabilities or illness (Bowen, 1966; Bowlby & Ainsworth, 2013; P. Christensen, 2004; Golan & Weizman, 2001; Lynch & Morley, 1995; McConkie-Rosell & Spiridigliozzi, 2004), six were on child health and development (Berman et al., 1994; Bronfenbrenner, 1986; Fosco & Grych, 2013; L. Jacobson, 2000; A. Sameroff, 2009; Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012), three were on the cost of rearing children (Anderson et al., 2007a; Apps & Rees, 2001; Becker, 2009), and the remaining one was on measuring health status outcomes in children (Annett, 2001).

These theories, conceptual frameworks, and models offered distinct but complementary lenses to see the ways that child health and development are intertwined with the health and well-being of family members, how children's illness and disability influence the family welfare and the family as a whole through complex and changing dependency relationships, and their potential implications on the inclusion of family spillover effects in pediatric economic evaluation of health-related programs. A detailed description and analysis of each theory, conceptual framework, or model within the context of family spillover effects presented in the following section.

3.3.3 Critical Appraisal of Included Theories, Conceptual Frameworks, and Models

Table 3-4 shows the quality assessment of included theories, theoretical frameworks, and models. The quality rating of included theories, conceptual frameworks, or models ranged from 1 to 4, with a mean score of 2.75. In general, the authors clearly stated how theories, conceptual frameworks and models were developed and explained the logical relationships between concepts, constructs and variables of proposed theories, conceptual frameworks, and models. The empirical evidence on theoretical claims or propositions and the validity of the proposed theory, conceptual frameworks or models were not apparent for the majority of included studies. Evaluating empirical evidence of theoretical claims or propositions and the validity of the proposed theory, conceptual frameworks or models in the respective field was challenging. Some of the included theories, conceptual frameworks, or models have made several theoretical claims or propositions, some of which have empirical evidence or/and been validated in the respective

field, and some do not. Moreover, some of the theories have been updated several times by the original or other authors, so it was difficult to track their empirical evidence and validation. Finally, included theories, conceptual frameworks, or models are from various disciplines. Having empirical evidence or empirically testing theoretical claims or propositions might not be standard practice. For instance, six included theories, conceptual frameworks, or models are from psychology, where testing for empirical evidence might not be standard compared to economics. Some qualitative researchers suggested examining the contribution of the included studies to the development of concepts or themes and overall theoretical framework (M. Dixon-Woods et al., 2005; Mary Dixon-Woods et al., 2006). They suggest that assessing the relevance of papers to the synthesis is more important than the quality of the appraisal. Further research should explore the development of the appropriate tools to examine the quality and/or relevancy of included theories, conceptual frameworks, or models.

3.3.4 Concepts and Synthesizing Argument Emerging from Review

Five concepts ultimately emerged from 19 synthesized constructs and 58 codes created through the CIS as being central to 'conducting economic evaluation from a family perspective.' The five concepts include (see Table 3-5): (1) The health and well-being of family members is interdependent, (2) Collective family costs, (3) Maximizing health and well-being, (4) The family is a unit of analysis, and (5) Factors influencing child health and development. A complete list of codes that emerged from the synthesis of evidence included in selected theories, conceptual frameworks, and models that led to respective synthesized constructs and concepts are presented in Tables 3-6 to 3-10.

The concept of 'The health and well-being of family members is interdependent' refers to the continuous bidirectional and changing dependency relationships between the child's health and development and the family's health and well-being. 'Collective family costs' reflect the idea that the cost of a child is the sum of consumption of market goods, services expenditures related to the child, and family member time cost (particularly, parent time cost) devoted to childcare. Family resources used in caring for a child with illness or disability cannot be separated from understanding how these resources are acquired, and the opportunity cost. 'Maximizing family health and well-being' informs that the family collectively combines their resources and time and

allocates efficiently to maximize the health and well-being of all family members, including children. ‘A family is a unit of analysis’ refers to using the family as a unit of analysis to evaluate the child’s health and well-being. Finally, ‘Factors that influence child health and development’ refer to family socioeconomic status, families’ cultural, religious beliefs and health practices and other social and environmental factors affecting child health and development. The following sections describe how these concepts and synthesized constructs emerged from included theories, conceptual frameworks and models are discussed in greater detail. A unique perspective on understanding child health and development in the family context is provided, and how these concepts inform incorporating family spillover effects in pediatric economic evaluation is presented.

3.3.4.1 Health and Well-being of Family Members is Inter-dependent

The idea that child health and development are inter-dependent with the health and well-being of the family members emerged throughout the selected theories, conceptual frameworks, or models. Six synthesized constructs emerged from codes that led to the concept ‘The health and well-being of family members is interdependent.’ The list of codes and synthetic constructs for this concept can be found in Table 3-6. The first synthesized constructs that emerged from the analysis and fitted within the interdependent health and well-being construct is the ‘bidirectional relationship.’ The notion that child development can be explained through the bi-directional relationship between the child and their parents is postulated by the transactional model of development and ecological systems theory (Bronfenbrenner, 1977, 1986; A. Sameroff, 2009; A. J. Sameroff, 1975; A. J. Sameroff & Chandler, 1975). It is not only the case that parenting behaviours can produce changes in child behaviours, but that child behaviours also influence parents’ behaviour and adjustment (Bronfenbrenner, 1986; A. J. Sameroff & Chandler, 1975). Bowlby’s attachment theory also views the relationship between caregiver and infant as dynamic, in that the infant’s response shapes the mother’s response and successively shapes that of the child (Bowlby & Ainsworth, 2013; Bretherton, 1992). The attachment patterns that children develop during infancy or childhood are influenced by how parents treat them and have a tremendous impact throughout their lives. In the sociocultural theory of development, Vygotsky discussed the roles of parents (adult caregivers) in shaping children’s learning and

development (Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012). It is only through social interaction and with the social guidance provided by adults (usually a caregiver) that children can acquire cognitive skills such as language, abilities, literacy, reasoning, problem-solving, and self-regulation.

The second synthesized construct, complex and changing relationships, demonstrate these reciprocal interactions that ensue within parent-child dyads are dynamic and change over time. For instance, the parent-child influence in the adolescent transitional period is different from the infant transitional period due to behavioural and emotional changes or because adolescents gain more autonomy and independence (A. Sameroff, 2009).

The third synthesized construct is a dynamic relationship. The health and well-being of children are inextricably linked to the family members' physical, emotional, and social health and vice-versa. The Bowen family system theory considered a family an emotional unit, where each family member strongly influences other family members' thoughts, feelings, and actions (Bowen, 1966). Similarly, Lynch took a holistic approach and discussed how a diagnosis of a disability of a child or medical disability of a child influences the well-being of family members and the family's lifestyle and future goals (Lynch & Morley, 1995). Fosco & Grych, in their conceptual model, described that parental well-being, the quality of the marital relationship and family functioning impact the parent-child interaction and, in turn, shape children's emotion regulation (Fosco & Grych, 2013). The degree of intensity of these effects depends on how closely a family member is linked to an emotional unit or the strength of the relationship (Bowen, 1966; Brown, 1999). Children are too young and/or lack the necessary cognitive, linguistic and communication skills to self-report health behaviours, or self-reported behaviours may not capture all dimensions of disease or disability. Annett proposed a conceptual framework on health outcome measurement, suggesting that researchers should include both children and parental subjective and objective experiences with the disease to assess the health outcomes of children with asthma (Annett, 2001). The conceptual framework also demonstrated how ineffective symptom appraisal could increase family stress.

In line with the view that there is a changing bi-directional relationship between the child and family member's well-being, economics theories, conceptual frameworks, and models have

described bidirectional relationships as ‘interdependent utilities.’ i.e., an individual’s subjective well-being depends on some measure of well-being of other individuals, which is the fourth synthesized construct. The parents value and derive utility not only from their own consumption but also from the utility of their children (Becker, 2009). Jacobson explains how a child’s health is important for parents’ health stock and parent investment in their health (L. Jacobson, 2000). In particular, the author considered each family member to be a producer of his/her health and the health of family members.

Furthermore, a few included theories, conceptual frameworks and models acknowledge the effect of genes in predicting child development and health, which is the fifth synthesized construct. For example, Becker discussed how genetic factors affect the demand for children and why parents prefer biological children over adopted children (Becker, 2009). Parents having biological children reduces parents’ uncertainty because they have more information about biological children's genetic constitutions and early environmental experiences than those obtainable from others. Christensen’s conceptual framework draws attention of examining the family history of illness and genetics in understanding the health and well-being of a child (P. Christensen, 2004). When a child is diagnosed with a genetic disorder, it becomes part of family identity (McConkie-Rosell & Spiridigliozzi, 2004). Furthermore, the Grossman model on which the Jacobson model is based claimed that children's health and intelligence partly depend on genetic inheritance (Grossman, 1982; L. Jacobson, 2000).

The final synthesized construct that emerged from the included theories, conceptual frameworks and models that fit within the construct of interdependent health and well-being is the ‘changing roles.’ As demonstrated in the abovementioned theories, conceptual frameworks, and models, it is evident that there is a continuous bidirectional and changing dependency relationship between the child’s health and development and family members’ health and well-being. Consequently, if unexpected events happen in the family, such as a child being diagnosed with a disability or chronic illness, the roles of family members will alter. The family system theory posits that if such an event ensues in a family and an ill member can no longer fulfill the familial obligations, another family member will automatically over-function to compensate for the dysfunction of the other who is sick temporarily (Bowen, 1966). These extra familial responsibilities will affect the

health and well-being of a family member who took the extra-familial obligations. Lynch and Morley agreed with this premise (Lynch & Morley, 1995). In their conceptual framework, when there is a child with a disability is in the family, parents' functions, and roles change. For example, parents will have less time for recreational and social activities and will need to modify career choices. Career ladders may be restricted because of the increased time required for caregiving. Eventually, these changes may influence the health and well-being of parents (Lynch & Morley, 1995).

3.3.4.2 Collective Family Costs

The second concept that emerged from the literature synthesis is related to 'collective family costs.' Table 3-7 shows nine codes and three synthesized constructs that led to this concept. Parent cost is the first synthesized construct that emerged from the synthesis of evidence from included studies. Several theories, conceptual frameworks and models asserted that parent time cost devoted to childcare should be included while estimating costs of the child and costs related to the child's illness or disability. Economics theories, conceptual frameworks, or models treat expenditures on children by parents as part of household production (Apps & Rees, 2001; Becker, 1981, 2009; L. Jacobson, 2000). Through household production, families produce children using market goods and services and parental time. Since the cost of parental time and household production differs among families, the total cost of producing and rearing children also differs from family to family. Thus, these theories emphasize that only by including costs associated with related re-allocation of parental time from market work and other household production activities such as sleep, leisure, and personal care to caring for children can one estimate the total cost of rearing children. Anderson's model includes costs related to family time (caregiving time, employment time, leisure time, and sleep time) to understand the dynamic economic burden of child disability (Anderson et al., 2007a). Similarly, Lynn and Morley's conceptual framework demonstrates that having a child with a disability in the family may reduce the parental time for leisure activities due to the increased time required for fulfilling caregiver responsibilities (Lynch & Morley, 1995). Finally, Annett's conceptual framework illustrates how an ineffective symptom appraisal can decrease parental job productivity (Annett, 2001).

The second synthesized construct is a ‘family cost.’ The idea that there is a dynamic relationship between family’s cost and child health and well-being appeared throughout the included theories, conceptual frameworks, or models. For example, Jacobson extended the Grossman health capital model (Grossman, 1972) to incorporate the family perspective (L. Jacobson, 2000) . The author considers the family as a producer of health where each family member is the producer of his/her own health and the health of other family members and therefore of his/her own income and wealth and the earnings of other family members. Increasing a child’s health capital by using some of the family wealth and parent time would reduce the sick time of a child and increase parental employment; therefore, family income would increase. Similarly, this dynamic relationship is illustrated by Anderson’s conceptual framework on the costs of caring for a child with a disability (Anderson et al., 2007a). Anderson and colleagues, in their model, assumed that families with more time available for employment would likely have more family income. Therefore, they may be able to spend money to meet the needs of a child with a disability, for example, spending on babysitting or special equipment needs or other services. On the other hand, the family that spends more time caring for the child will have less time for employment; hence lower family income and the family may not be able to meet the child’s health needs.

Finally, a third synthesized construct that emerged from the evidence and fit within the construct of a collective family in estimating child costs is ‘intra-family resource allocation’ which depends on two broad processes: the resource generation process and the resource distribution process (D. Thomas, 1990). Berman et al. described the household production of health (HPH) framework as a dynamic behaviour process in which households combine social, economic and health inputs to restore, maintain, and promote family members’ health (Berman et al., 1994). The HPH framework assumes that households (as a unit) know how to produce healthy children, and they make decisions based on the importance they place on having healthy children versus consumption of other market goods and services. Economics theories, conceptual frameworks or models depict the same idea. For instance, Apps and Rees describe the child’s cost as an outcome of intra-household resource distribution of consumption, that is, how much consumption of all market goods, including childcare, a household chooses to allocate on children and parental time in caregiving (Apps & Rees, 2001). In the ‘family as a producer of health’ framework, the family collectively decides and chooses the amount of market goods to

consume to maximize family lifetime utility (L. Jacobson, 2000). Finally, the Anderson model describes the family of a child with a disability making decisions to invest in a child's care (i.e. goods and services for a disabled child's care) based on family income, savings, and consumption of everyday goods and services (Anderson et al., 2007a).

3.3.4.3 Maximizing Family Health and Well-being

The third concept that emerged from theories, conceptual frameworks and models is related to the concept of 'Maximizing family health and well-being.' This concept is closely related to the abovementioned three concepts. Table 3-8 shows five codes and three synthesized constructs that led to this construct. The first synthesized construct that emerged from synthesizing evidence from included theories, conceptual frameworks, or models that inform this construct is 'maximizing family health and well-being.' The family health maximization is a concept that emerged from two theories. Berman et al.'s HPH framework place the household at the center of the health improvement process (Berman et al., 1994). The HPH framework considered households engaging in health-producing behaviours such as infant and child feeding practices, childcare, and treatment-seeking to restore, maintain and improve the health of all family members. These choices are constrained by the internal and external resources available to them, the prices of goods, and their own time. The family system theory considers the family as an emotional unit (Bowen, 1966). This emotional interdependence evolves to promote the cohesiveness and cooperation among family members required to reduce the family tension and maintain stability.

Economists have described maximizing family health and well-being in terms of 'family utility maximization,' which is the second synthesized construct. The theories and frameworks discussed above considered the family or the household as the producer of health that maximizes the family utility. For instance, Jacobson's framework considers that each family member derives utility from their own health and the consumption of other commodities as well as from family members' health and consumption (L. Jacobson, 2000) . As a result, they receive investment and consumption benefits from investing in the health of other family members. The family, therefore, invest in health "until the rate of marginal consumption benefits equals the rate of marginal net effective costs of health capital" (page 627) (L. Jacobson, 2000) .

The final synthesized construct is parental altruism. Becker, in his theories, described parents are altruistic toward children (i.e., parents' concern for the well-being of their own child). The utility of parents depends positively on the utility of their children. The parents' utility is maximized when all children attain the same level of maximum utility. Furthermore, although Bowen did not mention altruism in his family system theory, the author statement, "An emotional system operates with a delicately balances equilibrium in which each devotes a certain amount of being self to the welfare and well-being of others" (page 367) relates to the altruism discussed by Becker (Bowen, 1966).

3.3.4.4 Family is a Unit of Analysis

The fourth concept that emerged from the analysis related broadly to the concept of 'Family is a unit of analysis' to evaluate the child's health and well-being. Four synthesized constructs emerged from the synthesis of evidence from included theories, conceptual frameworks, and models (Table 3-9). These include: 1) the family is a producer of health, 2) the family is a system, 3) family decision making, and 4) a family-centered approach. Becker first devised the economic concept of a household production function. Families combine the resources they own, or they buy with their own time to produce 'household commodities,' i.e., the items that provide utility or well-being for family members (Becker 1991). Household commodities include child characteristics, such as school performance and social skills. The family is the producer of health, where each family member is the producer of his own health and the health of other family members and his own income and wealth and the income and wealth of other family members (L. Jacobson, 2000) . Berman et al. also used the Grossman health capital approach to develop the health production model. Placing the household at the center of health improvement process, the HPH approach explains the health behaviour of individuals resulting from their interaction with the social, economic and health system settings within which the household operates (Berman et al., 1994).

Scholars in psychology had begun to explore the family as a system long before economists did. In particular, the Bowen family system theory underscores the need to consider reciprocal influences among all members of the family unit in understanding child development (Bowen, 1966). Bowen considered a family as an emotional unit, where a change in one system will

automatically change in another part of the system, as illustrated by his quote, “each of us is best understood not as an individual psychological unit, but as a functional part of an emotional unit -- the family” (Bowen, 1978, p. 189). The basic unit of analysis in the ecological system model is the microsystem, which refers to the immediate and perspective environment of the child (the family and the school). The ecological system suggests taking a family perspective for understanding child development (Bronfenbrenner, 1977, 1986). Lynch and colleagues developed a conceptual framework for counselling children with disabilities and their families based on the family system, where all members are affected by any member’s actions (Lynch & Morley, 1995). Christensen’s health-promoting family framework emphasized that rather than focusing on linking to different types of the family (e.g., one or two-parent families), one should concentrate on the family as a whole and what they do every day as health practices (P. Christensen, 2004). Family system theories encourage us to think of the family as a whole. To understand family members’ health and well-being, one needs to focus on interactions between individuals in a family and between the family and the context(s) in which the family is embedded.

The third synthesized construct that emerged from the included theories, conceptual frameworks and models related to this concept was ‘family decision-making.’ Children are not independent decision-makers. They rely on their parents for their health care needs and healthcare resource consumption. Children with or without cognitive limitations depend on parents or caregivers for healthcare decision-making. Parents’ choices of health care services on behalf of their children may potentially impact the child’s development and health. Often, these decisions are made collectively as a family. Jacobson describes that decisions regarding investing resources in child health and investments in adults’ health and consumption of market goods are made within the family by parents (L. Jacobson, 2000) . In the Familial approach to the treatment of childhood obesity conceptual model, the authors assert that change (e.g., maintaining a healthy lifestyle in the family) should be delivered through parents to prevent obesity (Golan & Weizman, 2001). The parent serves both as a source of authority and a role model for the obese child. Furthermore, in the family system theory, Bowen stated that after family members become ‘system experts,’ and family could readjust itself without the help of an expert when a member in the family is again emotionally distressed (Bowen, 1966).

Last, the synthesized construct that fits within the concept 'Family is a unit of analysis' was using a family-centered approach. Several selected theories, conceptual frameworks, and models suggested using a family-centered approach to provide treatments or programs or assess health outcomes for children with chronic illness or disabilities. Golan and Weizman stressed the importance of developing intervention programs focused on the entire family for treating obesity in children (Golan & Weizman, 2001). They emphasized that efforts should be made to assist parents in adopting healthy eating behaviours in the family so that children will develop better eating and physical activity habits. Annett, in their framework, asserts that health outcome assessment for children with asthma should include dimensions related to the child's health, the family functioning and the environment, including parents' subjective and objective experiences with the disease (Annett, 2001). Similarly, the McConkie-Rosell et al. framework for Genetic Testing in Children posits that genetic counsellors should adopt a family-centered approach (McConkie-Rosell & Spiridigliozzi, 2004). That approach requires exploring the family's values and beliefs regarding genetic testing and coping behaviours and actively partnering with the family (parents) to identify ways to promote healthy interaction of information into a child's self-concept and facilitate positive adaptation of the child to the genetic information.

3.3.4.5 Factors Influencing Child Health and Development

The final concept that emerged from the synthesis of evidence from included theories, conceptual frameworks, and models is broadly related to external factors influencing child health and development (Table 3-10). These factors can be conceptualized into family socioeconomic characteristics, families' cultural and religious characteristics and environmental and societal characteristics. The idea that a child's health and development is influenced by family socioeconomic status and families' cultural and religious beliefs and various environmental factors, and their interactions appeared throughout the included theories, conceptual frameworks, and models. From the abovementioned concepts, it is evident that there are complex and changing dynamic relationships between children's health and development and the family members' health and wellbeing. It is also essential to understand that children and their parents are involved in many ecological milieus that are changing and changed by their participants and the effects that these multiple factors could have on the bi-directional parent-child relationship.

Bronfenbrenner explains that family income plays an important role in acquiring services required for sustaining the health and well-being of family members, including the development of the child (Bronfenbrenner, 1986). Becker's model suggests that the demand for children depends on the family income. An increase in family income generally increases the demand (parents wanting children) for children (Becker, 1981).

Lynch and Morley, in their model, suggest that it is important to be aware and plan an intervention based on the needs of children identified through the assessment of family culture, values and beliefs while counselling children with disabilities and their families (Lynch & Morley, 1995). Agreeing with Lynch and Morley, McConkie-Rosell & Spiridigliozzi also encourage exploring family values and beliefs regarding genetic testing while providing genetic counselling for children and their families (McConkie-Rosell & Spiridigliozzi, 2004). Christensen's model illustrates how a mother's and a child's health beliefs, behaviours and practices are linked (P. Christensen, 2004). In the familial approach to treating childhood obesity conceptual model, Golan and Weizman discussed how the parents' culture, attitudes, and beliefs shape children's eating habits (Golan & Weizman, 2001).

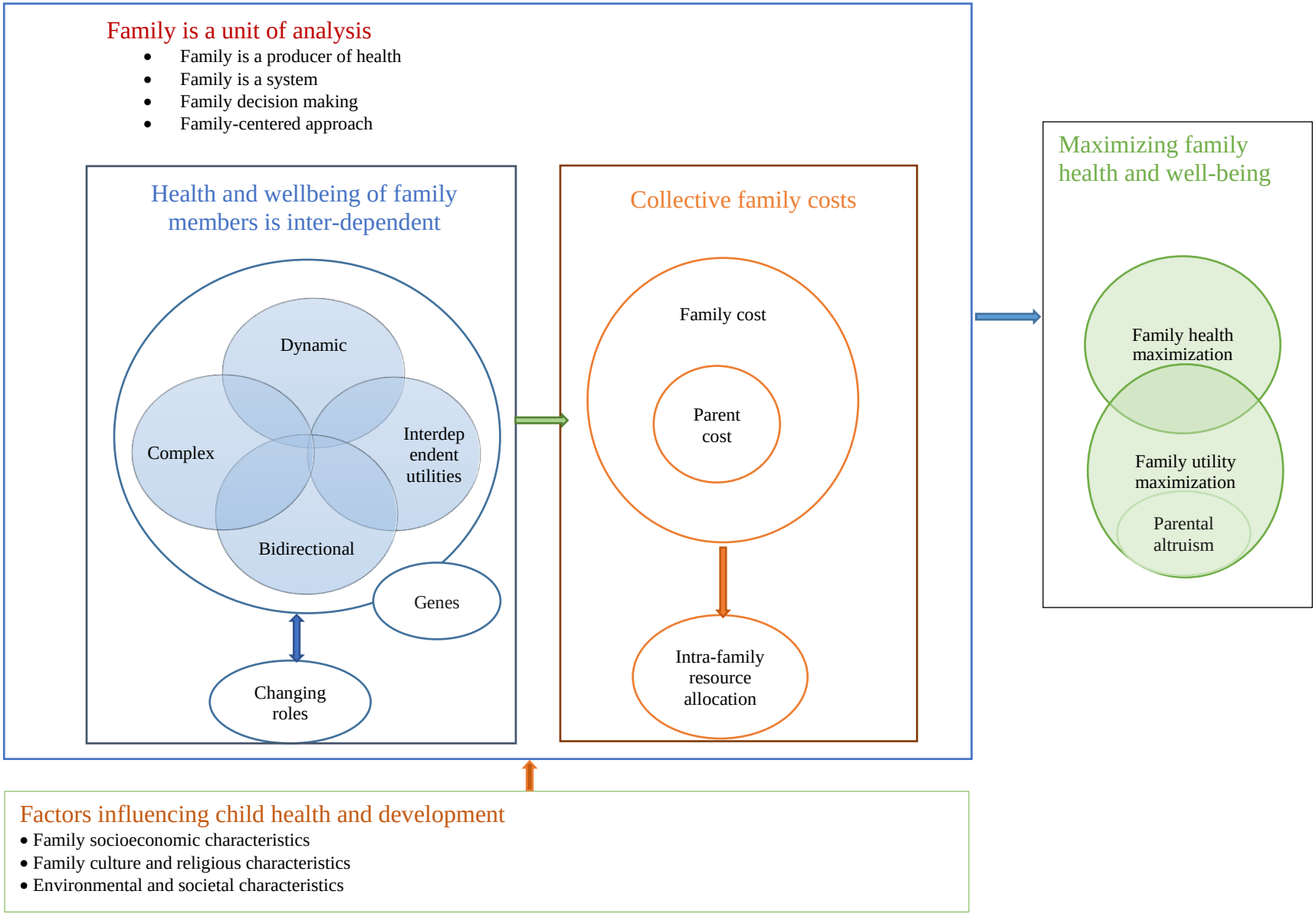
Regarding environment characteristics, the transactional model asserts that the child's development can be described through the reciprocal interchanges between the child and the environment. These exchanges are recurrent, and the child's development cannot be understood without examining the interactions between the child's characteristics and contextual variables over time (Fanti, 2011; A. Sameroff, 1975, 2009; A. J. Sameroff & Chandler, 1975). Bronfenbrenner expanded these ideas by proposing that understanding child development also requires consideration of ecological effects, that is, the multiple social contexts in which the child is embedded and transactional effects (Bronfenbrenner, 1986). The ecological systems theory posits that child development occurs within and between the different ecological settings, and within and between micro system (the immediate setting in which the child operates, e.g., family, school, and peers), the meso system (interaction between microsystems), the exosystem (the neighborhood and community), and the macro system (the values and beliefs of the culture of the society) (Bronfenbrenner, 1977, 1986; Fanti, 2011).

3.3.5 A Theoretical Framework: Conducting Economic Evaluation from a Family Perspective

Figure 3-2 provides an overview of the concepts that emerged from the critical interpretative synthesis and how these concepts are logically related to form a theoretical framework 'conducting economic evaluation from a family perspective.' In figure 3, boxes represent concepts, and arrows represent the relationships among them. The inner circles and/or texts inside boxes represent synthesized constructs and the relationship among them as described in section 3.3.4.

For this model, *the family* is defined as persons living in the same dwelling who are related to a child (≤18 years) with chronic illness or disability by blood, adoption, or foster care and who are closely involved in the day-to-day operations of the household and who support other family members. The family members could include parents, stepparents, siblings, grandparents, or extended family members living in a household. It also includes lesbian, gay, bisexual, transgender, queer and questioning, and two Spirit (LGBTQ2S)+ families, chosen families, single parents and people living alone.

Figure 3-2 A Theoretical Framework for Conducting an Economic Evaluation from a Family Perspective



The proposed theoretical framework using a family approach to measuring health consequences recognizes the ineluctable interdependency between a child's development, health and well-being, and other family members' health and well-being as demonstrated by selected interdisciplinary theories and conceptual frameworks or models. The concept of interdependent health and well-being of family members is closely related to the concept of a collective family approach to estimating child costs. Given the interdependent relationship in health and well-being between the child and family members, it impacts the economic well-being of family members when the child is ill. For instance, parents are likely to re-allocate their time from employment and household activities to care for the affected child. Furthermore, the family may need to reduce their spending on market goods and services and allocate funds towards the treatments for the child. The concepts of health and well-being of family members is interdependent, and family costs inform that the child's health and well-being are inextricably embedded in the family system and can never be fully understood independently of that system. And therefore, family as (is) a unit of analysis is necessary to understand a child's health and well-being. The concept of maximizing the health and well-being of family members speaks to the idea that the health and well-being of the child and family members is interdependent and therefore, the decision to invest in the child health and treatment is made by parents considering the health and well-being of all family members. It maximizes the health and well-being of all family members based on available internal resources, external resources, and family member time (particularly parent time). Health investment decisions on the child's health and well-being also depend on the prices of the market goods and services and expenditures on the health of other family members. Finally, family socioeconomic status, culture, religious beliefs other social and environmental factors influence child health and development.

Conducting pediatric economic evaluation from a family perspective requires the family as the unit of analysis to evaluate the child's health and economic and/or well-being where family costs and consequences related to a child's illness or disability are derived from all family members and incorporated into the analysis of economic evaluation. A family perspective to evaluate costs and consequences of the child's health intervention highlights the concept that child health and development are complex and, further, that they are integrated with family members' health and well-being. It assumes that individual family members exercise continuous and reciprocal

influences on one another. It is important to note that unlike for estimating child costs, selected theories, conceptual frameworks, and models did not explicitly claim that researchers should adopt a collective to measure health consequences while evaluating health consequences. A collective approach to measuring health consequences from family members recognizes the ineluctable interdependency between the child's development, health and well-being and other family members' health and well-being.

3.3.5.1 An Approach of Conducting Cost-Utility Analysis of Pediatric Interventions from a Family Perspective

Economic evaluation in healthcare assesses the efficiency of allocating resources to interventions that may improve patients' health outcomes. The vital part of conducting an economic evaluation is to identify, measure and value costs and consequences of alternative programs or interventions being considered (Drummond et al., 2015). There are primarily four types of economic evaluation methods. They are cost-benefit analysis (CBA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), and CUA (Drummond et al., 2015). A key difference across the different types of economic evaluation is how the outcome or consequence is measured and expressed. For instance, in the CBA, the benefit or consequence of the health intervention is expressed in monetary terms. In contrast, CEA measures the health consequences of the health intervention in a single natural unit (such as life-years gained, cases averted, or cases detected), and CUA (a specific type of cost-effectiveness analysis) measures the health consequences using a generic measure of health status that considers the effects on both mortality and morbidity, such as disability-adjusted life year (DALYs) and quality-adjusted life-years (QALYs) (Drummond et al., 2015). The above proposed theoretical framework ‘conducting economic evaluation from a family perspective’ could be used to incorporate spillover effects and/or develop empirical methods to incorporate spillover effects for all four types of economic evaluation.

The QALY-based CUA is recommended by many health technology assessments (HTA) agencies in high-income countries (HICs). For instance, organizations such as the Canadian Agency for Drugs and Technologies and the National and Care Excellence (Canadian Agency for Drugs and Technology in Health (CADTH), 2017; National Institute of Health and Sciences (NICE), 2013) that are responsible for providing information on the efficiency of drugs and

medical devices to healthcare decision-makers in Canada and the UK require CUAs of alternative treatments or interventions. The CUA is also the recommended analytic technique in other publicly funded healthcare systems such as in Australia (PBAC, 2016) and the Netherlands (ZorginstituutNederland, 2016).

The present approach is explicitly focused on the two concepts (1) A collective family approach in estimating the child costs and (2) a collective family approach in estimating the consequences related to a child's illness or disability of the theoretical framework described in the section 3.3.4. In the case of the CUA, a collective family approach in estimating the child costs and a collective approach in estimating QALYs. The present approach is described as follows. Section 3.3.5.1.1 describes the different elements (variables) of family costs spillover effects in a three-person household comprising a child with chronic illness and how the family cost could be estimated using an *isolated method* from a family perspective. Section 3.3.5.1.2 describes the elements of family health spillover spillovers in the context of health utility in a three-person household comprising a child with chronic illness and how the family QALYs could be estimated using the *inherent method*. The different elements of family cost and health spillover effects in a three-person household were assumed or identified based on the conceptual framework presented in Chapter 1 and methods used by researchers to measure and incorporate the family health spillover effects in Chapter 2. The conceptual framework in Chapter 1 describes how the family health and cost spillover effects occur in the family using the evidence from existing literature. The systematic review Chapter 2 summarizes the different methods used by researchers to measure and incorporate family health spillover effects on caregivers and/or family members in pediatric and maternal-perinatal CUAs. For instance, several pediatric and maternal-perinatal CUAs included in Chapter 2 recognized given the dynamic, complex, and changing dependency relations between a child's health and well-being and parents' health and well-being, it is challenging estimate increments or decrements on an individual family member's health utility due to a child's adverse health state as isolated quantities. Therefore, an alternative method an inherent method for estimating family heath spillover effects is proposed. We describe the proposed method in Section 3.3.5.1.2. Finally, section 3.3.5.1.3 illustrates how the cost-utility of pediatric interventions can be operationalized from a family perspective,

considering the family costs and health spillover effects using the data from a hypothetical randomized controlled trial.

For this model, *the family* is defined as persons living in the same dwelling who are related to a child (≤18 years) with chronic illness or disability by blood, adoption, or foster care and who are closely involved in the day-to-day operations of the household and who support other family members. The family members could include parents, siblings, grandparents, or others. For simplicity, we assume a three-person household consisting of a child with chronic illness or disabilities, a parent1, and a parent2.

3.3.5.1.1 Family Costs from a Family Perspective

For simplicity, let us assume that the family comprises a child with chronic illness or disability, C, a parent1, P1, and a parent2, P2. In constructing a model for estimating the family cost spillover from a family perspective, the following two assumptions are made: (1) parent1 and parent2 allocate their time to the general household activities, work, leisure, and childcare, and (2), the family collectively makes decisions to invest in a child's health based on available resources, including internal resources, external resources, and family members' time, particularly the parents' time. The total costs of a child's illness or disability from the family perspective, C_F, theoretically would be:

$$C_F = (C_c + C_{P1} + C_{P2} + C_h) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots. \text{(i)}$$

Where, C_c is the costs of a child's (medical and non-medical) resource use and the current and future opportunity cost of a child's productive time; C_{P1} is the total costs incurred by parent1, P1, due to a child's illness or disabilities, including direct healthcare costs, direct non-healthcare costs, out-of-pocket costs, and productivity costs;, C_{P2} is the total costs incurred by a parent2, P2, due to a child's illness or disabilities; and C_h is household expenditures related to the child's illness or disabilities. This approach of incorporating the family cost spillover effects can be referred to as an *isolated method*. An isolated method to including the family cost in pediatric economic evaluation would require the measurement of costs separately for each parent as an isolated quantity to be summed with the costs of the child's medical or/and non-medical resource use, the current and future opportunity cost of a child's productive time and household

expenditures related to the child's illness or disabilities. An isolated method is usually used in pediatric economic evaluations to measure and include the family costs spillover effects of caregivers and/or parents when spillover costs are included. Traditionally these would include parents'(caregivers') productivity costs and parents' out-of-pocket costs of for medical or non-medical services for the child's health (Drummond et al., 2015; Pike & Grosse, 2018). For instance, in equation (i), C_{P1} represents the costs incurred by parent1 due to a child's illness or disability.

In the present method, the family cost for parent1, C_{P1} , can be further broken down into (1) productivity costs associated with loss of employment, reduced hours for paid or unpaid labour, or loss of leisure time due to caregiving for parent1, 2) direct healthcare and non-healthcare care costs for parent1 for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disabilities, 3) out-of-pocket expenditures or co-payments by parent1 for medical or non-medical services for the child's health, 4) out-of-pocket expenditures or co-payments of parent1 for medical or non-medical services used by parent1 for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disability, and 5) household expenditures related to the child's illness or disabilities (such as buying special equipment) for parent1. Similarly, the family cost for parent2 can be broken down into different components. The sum of the last three terms C_{P1}, C_{P2} and C_h, in equation (i) represents the family cost of a child's illness or disability in a three-person household. These three terms consist of the following items:

1. Productivity costs associated with loss of employment or reduced hours for paid or unpaid labour or loss of leisure time due to caregiving for parent1, P1.
2. Productivity costs associated with loss of employment or reduced hours for paid or unpaid labour or loss of leisure time due to caregiving for parent2, P2.
3. Out-of-pocket costs or co-payments of parent1, P1, and/or parent2, P2, for medical or non-medical service for the child's health.
4. Other household expenditures related to the child's illness or disabilities
5. Out of pocket costs or co-payments of parent1, P1, and/or parent2, P2, for transportation and lodging for the child to receive medical or non-medical services (such as social services, rehabilitation, education, and others)

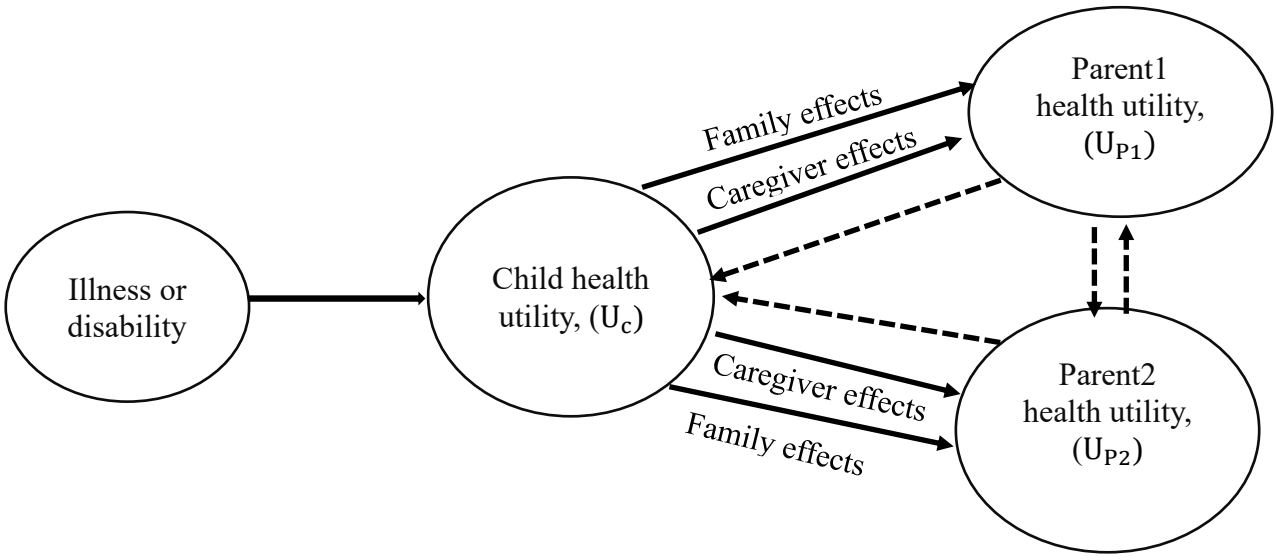
6. Direct healthcare and non-healthcare care costs for parent1, P1 for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disabilities.
7. Direct healthcare and non-healthcare care costs for parent2, P1, for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disabilities
8. Out of pocket costs or co-payments of parent1, P1, for medical or non-medical service used by a parent1, P1, for their health and well-being as a direct result of caring for a child with chronic illness or disability.
9. Out of pocket costs or co-payments of parent2, P2, for medical or non-medical service used by parent2, P2, for their health and well-being as a direct result of caring for a child with chronic illness or disability.

In some cases, items one to five are currently included in pediatric CUAs that include recommended spillover costs conducted from a societal perspective (Ungar, D'Cruz, et al., 2018). However, direct healthcare and non-healthcare care costs for parent1 and parent2 as a direct result of caring for and caring about a child with chronic illness or disabilities and out-of-pocket costs or co-payments of parent1 and parent2 for the use of their medical or non-medical services for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disability are excluded (items six, seven, eight and nine). Table 3-11 summarizes costs elements included for public healthcare payer, family, and societal perspectives.

3.3.5.1.2 Family Health Utility from a Family Perspective

Let us assume the same three-person household comprising a child with chronic illness or disability, C, parent1, P1, and parent2, P2. Figure 3-3 represents relationships between illness or disability, child's health utility and parents' (parent1 and parent2) health utility. As shown in Figure 3-3, a chronic illness or disability directly affects a child's health utility, U_c. The change in the health utility (utility decrement or disutility) of a child due to a chronic illness or disability has direct effects on the health utility of parent1, U_{P1}, and parent2, U_{P2}. The direct effects on parents' health utility stem family effects and caregiving effects (Bobinac, Van Exel, et al., 2010;

Figure 3-3 Relationships between Illness or Disability, Child's Health Utility and Parents' Health Utility



The solid arrow indicates a direct effect, and the dashed arrow indicates an indirect effect.

Brouwer, 2019). Family effects in parents' family members occur due to witnessing the suffering or worse health state of a loved one, a child, 'caring about others.' Caregiver effects occur in parents due to providing care for a child with chronic illness or disability caring for others. Family effects and caregiver effects are discussed in detail in chapters 1 and 2.

Parents experiences increments and/or decrements in their health utility. Increments in parental health utility can occur through feelings of caring for and being appreciated by the cared-for child and other family members (Bobinac, Van Exel, et al., 2010, 2011). Conversely, decrements in parental health utility can occur through caregiving due to performing physically or emotionally demanding care tasks, often over long periods and witnessing the suffering or worse health state of a loved one, a child. Moreover, indirect effects (as represented by the dashed arrow) can occur in a child health utility, U_c, due to decrements or increments in parents' s health utility due to a child's disease or disability (Bobinac, Van Exel, et al., 2010, 2011). Finally, indirect effects can occur in parent1 health utility, U_{P1}, due to decrements or increments in parent2 health utility, U_{P2}, because of a child's disease or disability. Similarly, indirect effects occur in parent2 health utility, U_{P2}, due to decrements or increments in parent1 health utility, U_{P1}, because of a child's disease or disability. Therefore, the total effects of an adverse health state of a child in terms of health utility would be the sum of the following.

1. Direct effects of the disease or disability on the child utility
2. Decrements or increments due to caregiving and family effects (caring about others and caring for others) in parent1's health utility due to a child's disease or disability
3. Decrements or increments due to caregiving and family effects (caring about others and caring for others) in parent2's health utility due to a child's disease or disability
4. Indirect effects on a child's health utility due to decrements or increments in parent1's health utility due to a child's disease or disability
5. Indirect effects on a child's health utility due to decrements or increments in parent2's health utility due to a child's disease or disability
6. Indirect effects on parent1's health utility, due to decrements or increments in parent2's health utility because of a child's disease or disability
7. Indirect effects on parent2's health utility due to decrements or increments in parent1's health utility because of a child's disease or disability

Terms two to seven jointly represent the family health spillover effects on parent1 and parent2 due to a child's illness or disability. Items two to seven, in theory, can be measured using *the isolated method* proposed above for incorporating the family costs spillover. However, several practical challenges exist in measuring the family health spillover effects as the sum of isolated quantities. Some of these challenges are described in the subsequent paragraphs.

Given the dynamic, complex, and changing dependency relationships between a child's health and well-being and parents' health and well-being, estimating increments or decrements (disutility), in other words, gain or loss in HRQoL, on individual parents' health utility due to a child's adverse health state as isolated quantities is challenging. Several practical challenges exist in measuring the family health spillover effects as the sum of isolated quantities. First, establishing the causality of the relationships between a child's health and family members' health and wellbeing is very complex because of the dynamic and changing dependency relationship between a child's health and family health. For instance, for the parent who provides caregiving, does the strain of providing care led to a reduction in health and wellbeing on the parent, or does the parent with pre-existing health problems who becomes a caregiver perceive their care task as being more straining than parents of healthy children. To estimate disutility associated with having a child with chronic illness and disability accurately, one would need to

control for the family member (s) characteristics that affect the health utility separately from the child's illness or disability. One way to estimate disutility would be to measure and compare the health utilities of the family member(s) with a child with chronic illness or disability with the health utilities of a family member (s) with a healthy child. A key challenge is to ensure appropriate comparison groups (families) that do not have a child with chronic illness or disability to be able to correctly estimate attributable disutilities. It would not be easy to do so for each family member in the family. Furthermore, research has demonstrated that the family health spillover effects vary with the type and severity of the child's health condition and the family member's/caregiver's relationship to the child (Lavelle et al., 2014; D. Lee, Kim, & Devine, 2022; Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). Consequently, to measure an unbiased estimate of family health spillover effects for each childhood disease and condition, researchers need to find an appropriate control group and estimate the family health spillover effects for each member in the family. If study designs are not designed appropriately, it will be difficult to establish if an observed change in a family member's health utility is due to a child's chronic illness or disability, and the observed association may not be causal. Finally, existing health utility methods (indirect and direct elicitation) methods are not well designed to measure the disutility alone (Ungar, D'Cruz, et al., 2018; Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). These challenges are discussed in detail in Chapter 2.

Thus, an alternative approach, an *inherent method* of including family health spillover effects, is proposed. An inherent *method* of incorporating family health spillover effects suggests that the health utility scores of a family member include the impact of a child's illness or disability on the respective family member and the family member's underlying health state utility. Elderly parents or grandparents who are caregivers are likely to have chronic health conditions simultaneous with their caregiving responsibilities; therefore, their health utility scores will reflect a combination of both effects. This approach requires calculating each family member's health utility and then estimating QALYs independently and then summing the QALYs of each family member to estimate the family QALYs.

For simplicity, let us assume that the family comprises a child with chronic illness or disability, C, a parent1, P1, and a parent2, P2. In a three-person household, an inherent approach of incorporating family health spillover effects would begin with measuring the current health state

(health utility) of parent1 and parent2. The estimated health utilities for parent1 and parent2 for a current health state reflects parent1's and parent2' s current HRQoL, and, therein, family health spillover effects due to a child's illness or disability as well. Second, the QALY for each family member would be estimated individually for the child, parent1 and parent2. For instance, as illustrated in equation ii, QALYs of parent1 for a single health state, $\mathrm{QALY}_{\mathrm{P1}}$, can be estimated by multiplying the number of life-years a parent1 spends within a particular health state by the health utility that reflects the HRQoL in that state where U_{P1}represents parent1, P1, health-state utility weight and LY $_{\mathrm{P1}}$, represents the life years spend in the health state for parent1, P1. The health state is the status or the state of an individual's health at a particular time. Examples of health states for an individual could be progression-free, post-progression and dead. For a study with multiple health states within in a given time horizon, QALYs of parent1,$\mathrm{QALYs}_{\mathrm{P1}}$, can estimated by summing of QALYs across health states within in a given time horizon, as illustrated in equation (iii). Where, n represents the number of health states within a given time horizon, $\mathrm{U}_{\mathrm{P1}j}$ is the parent1 utility during the *j*th period and LY $_{\mathrm{P1}j}$ represents the life years spend in health states within in given a time horizon. Finally, the family QALYs in a three-person household consisting of a child with chronic illness or disability within a given time horizon, parent 1 and parent2, $\mathrm{QALYs}_{\mathrm{F}}$ as shown in equation iv, could be theoretically estimated by summing the QALY for a child, $\mathrm{QALY}_{\mathrm{SC}}$, QALY for a parent1, $\mathrm{QALY}_{\mathrm{SP1}}$, and QALY for parent2, $\mathrm{QALY}_{\mathrm{SP2}}$.

$$\mathrm{QALY}_{\mathrm{P1}} = \mathrm{LY}_{\mathrm{P1}} \times \mathrm{U}_{\mathrm{P1}} \quad \text{(ii)}$$

$$\mathrm{QALYs}_{\mathrm{P1}} = \sum_{j=1}^{n} \mathrm{U}_{\mathrm{P1}j} . \mathrm{LY}_{\mathrm{P1}j} \quad \text{(iii)}$$

$$\mathrm{QALYs}_{\mathrm{F}} = (\mathrm{QALYs}_{\mathrm{C}} + \mathrm{QALYs}_{\mathrm{P1}} + \mathrm{QALYs}_{\mathrm{P2}}) \quad \text{(iv)}$$

As mentioned above, we assumed a three-person household consisting of two parents and a child with chronic illness and disability for illustrative purposes. The proposed model for conducting cost utility analysis from a family perspective can be extended to multiple persons (more than three persons). For instance, the family comprises a child with chronic illness or disability, a healthy sibling, and parents. The total costs of a child's illness or disability from a family

perspective theoretically would be the sum of the cost for the index child with chronic illness or disability, the direct healthcare costs, direct non-healthcare costs, out-of-pocket costs, and productivity costs for the unaffected (healthy) siblings due to the index child's illness or disability and the direct healthcare costs, direct non-healthcare costs, out-of-pocket costs, and productivity costs for parents due to the index child's illness or disability. Similarly, the family QALY would be the sum of the QALY of an index child with illness or disability, the QALY of an unaffected sibling and QALY of parents.

3.3.5.1.3 Conducting Cost-utility Analysis of Pediatric Intervention from a Family Perspective: An Illustrated Example

The implementation of alternative health interventions or changes in care to improve the health and well-being of a child affects the health of the child receiving the health intervention and the health and well-being of family members in different ways. For instance, this could be because an intervention improves a patient's mobility and ability to perform daily activities compared to another option, consequently reducing parents' caregiving loads. One or both parents may return to work, decreasing the productivity costs related to work time loss in the intervention group. Moreover, there could be a reduction in medical or non-medical services used by the parent(s) for their health and well-being as a direct result of caring for and caring about a child with chronic illness or disabilities, thereby decreasing the direct health and non-healthcare costs. On the other hand, because of an improvement in the health utility of the child due to intervention compared to another option, there could be an improvement in the health utilities of parents. Finally, there could be indirect effects on the child's health utility and parents' health utilities, as described in Figure 2. The changes in the patient's health utility and associated changes in health utilities of parents (family health spillover effects) and costs for parents (family cost spillover effects) due to an intervention compared to another are essential components for estimating the full incremental costs and consequences of an intervention.

In economic evaluation, the primary goal is to inform decision-makers on comparative healthcare interventions incremental costs and incremental effectiveness to maximize net benefits from available and constrained resources (Drummond et al., 2015). The following sections describe how the cost-utility of pediatric interventions can be conducted from a family

perspective considering the family costs and health spillover effects using the data from a randomized controlled trial (RCT).

For simplicity, let us assume we want to conduct a CUA within an RCT comparing treatment A and standard care S from a family perspective. Let us assume one hypothetical patient among the group of patients randomized to receive treatment A, and his/her family comprises a parent1, P1 and parent2, P2. Another hypothetical patient was randomly assigned to receive standard care, and his/her family comprises parent1, P1 and parent2, P2. In this example, each patient and their parents' health utilities were measured: at baseline, six months, and nine months. Health utilities were measured using the CHU-9D for the child and parents using HUI-2 (self-reported). Health utilities at these time points were, respectively, 0.68, 0.78, and 0.88 for the child receiving the treatment A, and 0.78, 0.83 and 0.89 for parent1 of the child receiving the treatment A and 0.70, 0.80 and 0.90 for the parent2 of the child receiving the treatment A. Patient-level QALYs are typically estimated by applying the area-under-the-curve (AUC) method, which is implemented by summing the areas of the geometrical shapes obtained by linearly interpolating between health utility scores over the study period (Whitehead & Ali, 2010). The QALY for the child receiving the treatment using the area-under-the-curve (AUC) method would be 0.57 QALY, as illustrated in equations iv and v.

$$\mathrm{QALY(A)}_{Ci} = \left[\frac{(health\ utility\ score\ at\ baseline + \ health\ utility\ score\ at\ six\ months)}{2} * \frac{6}{12} + \frac{(health\ utility\ score\ at\ six\ months + \ health\ utility\ score\ at\ nine\ months)}{2} * \frac{3}{12}\right] \quad \text{(iv)}$$

$$\mathrm{QALY(A)}_{\mathrm{Ci}} = \left[\frac{(0.68 + \ 0.78)}{2} * \frac{6}{12} + \frac{(0.78 + 0.88)}{2} * \frac{3}{12}\right] \quad \text{(v)}$$

Where, $\mathrm{QALY(A)}_{\mathrm{Ci}}$ is QALY for the child, i, receiving the treatment A.

The QALY for parent1 and parent2 of the child receiving the treatment using the area-under-the-curve (AUC) method would be 0.62 and 0.59. The total family QALY for the treatment over the 9-month study period would be 1.78.

$$\text{FamilyQALY(A)}_{\text{Ci}} = (0.57 + 0.62 + 0.59) \ldots\ldots\ldots\ldots (v)$$

A similar approach could be taken to estimate the family QALYs for other patients and their parents in treatment A. The mean total QALYs per family in treatment can be estimated. An identical approach could be taken to calculate the mean total QALYs per family in the standard care. The estimated the mean total QALYs per family in treatment A, $\text{Family QALYs}_{\text{A}}$, and standard care, $\text{Family QALYs}_{\text{S}}$, can be used to estimate the incremental (differential cost) mean total QALYs per family, $\Delta\text{Family QALYs}$.

$$\Delta\text{Family QALYs} = \text{Family QALYs}_{\text{A}} - \text{Family QALYs}_{\text{S}} \ldots\ldots\ldots\ldots (vi)$$

For CUAs taking a lifetime horizon, the QALY for each family member can be estimated by measuring associated health utilities over the lifetime and using the remaining average life expectancies for each family member included. The CEA practice guidelines across the world recommend using a time horizon sufficiently long to capture all costs and outcomes – such that a lifetime horizon in the reference case analysis.

The following five assumptions were made in constructing an approach for estimating family health QALYs from a family perspective. These assumptions must be made while conducting a cost-utility analysis from a family perspective.

1. *Assumption 1: One full year of perfect health gained counts as one QALY regardless of the individual (family member)*. This implies that a QALY is independent of age. For example, in the above hypothetical example, gain in a single QALY due treatment for a five-year-old child is equivalent to a single QALY due to the treatment for a 35-year-old parent1, P1.
2. Assumption 2: *A QALY gained is a QALY gained, no matter how it is achieved*. For instance, in the above hypothetical example, over a standard time, a gain of 0.5 QALY for a child is equivalent to a gain in QALY of 0.25 for two parents (parent1 and parent2).
3. Assumption 3: *A QALY generated from different preference- based HRQoL can be summed across family members, including a child, to determine the family QALYs*. For instance, in the abovementioned hypothetical example, we assumed that the QALYs generated from HUI-2 for parents and CHU-9D for children are of the same nature and

meaning and can be summed even though they are elicited from different family members and produced from two different preference-based HRQoL instruments. The assumptions one to three are fundamental assumptions inherent in CUA (Drummond et al., 2015; Torrance & Feeny, 1989; Weinstein, Torrance, & McGuire, 2009).

4. Assumption 4: *The family health utility recognizes the interdependence of individuals within the family.* That is, the health and well-being of each family member are inextricably linked, and each family member is a producer of their own health and the health of other family members. Literature in health economics includes theoretical models that illustrate how a family member produces his/her own health and other family members' health (L. Jacobson, 2000).
5. Assumption 5: *The family health utility is a function of the health states of each family member*. The change (increment or decrement) in the health utility of one family member causes the change in the health utility (increment or decrement) of other family members.

3.4 Discussion

The idea that changes in the health and well-being of a child may have profound consequences (positive or negative) on the health and well-being of being of family members has been recognized for some time in health economic literature. However, family health spillover effects are often ignored in the economic evaluation of child health interventions leading to potential sub-optimal decision making. Theoretical frameworks and empirical methods on integrating family spillover effects into pediatric economic evaluation are not well elucidated to date. This study identified and synthesized 16 existing theoretical frameworks, conceptual frameworks, and models that support the consideration of family spillover effects in understanding child health and development or emphasized using the family (or household) approach to understand the child's health and development and provide care for children. A theoretical framework 'conducting economic evaluation from a family perspective' was proposed using insights from identified theories, conceptual frameworks, and models. Finally, based on the proposed theoretical framework, a model for incorporating family health and cost spillover effects in cost-utility analysis, a particular type of economic evaluation was proposed.

The subsequent sections first briefly synthesize the included theories, conceptual frameworks, and models. Section 3.4.1. describe the proposed theoretical framework for conducting an economic evaluation of pediatric intervention from a family perspective and associated equity concerns in considering family spillover effects in pediatric economic evaluation. Section 3.4.2 briefly describes an approach for conducting a cost-utility analysis of pediatric interventions from a family perspective and specific challenges in adopting the proposed model for cost-utility analyses. Section 3.4.3 presents the limitations of this study, and finally, section 3.5.4 concludes Chapter 3.

3.4.1 Synthesis of the Included Theories, Conceptual Frameworks, and Models

It is evident from findings that scholars in developmental psychology had begun to explore the interdependence of a child's health and development with the health and well-being of family members and family as a unit of analysis in understanding a child's health and development and providing care for children with mental illness long before scholars from other disciplines. The included theories, conceptual frameworks and models can be summarized as follows in the context of family spillover effects. First, a significant similarity among included theories, conceptual frameworks and models was the priority given to the bidirectional and changing relationships between the child and family members when understanding the child's development, health and costs (Anderson et al., 2007a; Annett, 2001; Apps & Rees, 2001; Becker, 2009; Berman et al., 1994; Bowen, 1966; Bronfenbrenner, 1986; P. Christensen, 2004; Fosco & Grych, 2013; Golan & Weizman, 2001; L. Jacobson, 2000; McConkie-Rosell & Spiridigliozzi, 2004; A. Sameroff, 2009; Lev Semenovich Vygotsky, 1980). Second, the majority of included theories, conceptual frameworks, and models emphasized using a family as a unit of analysis to evaluate children's health and well-being and plan and deliver services to children with chronic illness and disabilities (Berman et al., 1994; Bowen, 1966; Bowlby & Ainsworth, 2013; Bronfenbrenner, 1986; P. Christensen, 2004; Golan & Weizman, 2001; L. Jacobson, 2000; A. Sameroff, 2009). Third, all economics and a few health service research theories, conceptual frameworks, and models suggested using a collective approach (that includes the costs of parental time to caring for a child, household costs related to a child, the costs of a child's medical and non-medical resource use and the current and future opportunity cost of a child's

productive time) to estimate the total costs and the burden of a child's illness and/or have taken such an approach in their analyses estimating the total costs of a child's illness or disability (Anderson et al., 2007a; Apps & Rees, 2001; Becker, 2009; L. Jacobson, 2000). Finally, the authors of included theories, conceptual frameworks, and models asserted that child development and health could not be understood without considering the external environment in which children grew up (Berman et al., 1994; Bronfenbrenner, 1977, 1986; McConkie-Rosell & Spiridigliozzi, 2004; A. Sameroff, 2009; A. J. Sameroff & Chandler, 1975). The family is affected by external factors such as the neighborhood, the community, and access to health care and social services. For instance, children may learn social skills in the family context, but children's peer relationships may be influenced by the family's (parents') choice of neighborhood, community, and schools. These ideas were integrated into most identified theories, models, and frameworks.

3.4.2 Conducting a Pediatric Economic Evaluation from a Family Perspective

Previous work has have called for a family or household perspective in the pediatric economic evaluation, but details were not elucidated (A. Jacobson & Fried, 1998; Lisa A Prosser, J. K. Hammitt, & R. Keren, 2007b; J.M. Tilford & N. Payakachat, 2015; Ungar, 2011). Currently there are three proposed theoretical frameworks for incorporating the spillover effects (Labelle & Hurley, 1992; Basu & Metlzer, 2005; Al-Janabi et al., 2016). Using insights from interdisciplinary theories, conceptual frameworks and models on the child's health and development, this study developed a comprehensive theoretical framework to include family costs and health spillover effects in pediatric economic evaluation. Five concepts that emerged from the analysis as being central to 'conducting economic evaluation from a family perspective' are (1) The health and well-being of family members is interdependent, (2) Collective family costs, (3) Maximizing health and well-being, (4) The family is a unit of analysis, and (5) Factors influencing child health and development. The presented theoretical framework 'conducting economic evaluation of pediatric economic evaluation from a family perspective' requires the family as the unit of analysis to evaluate the health and well-being of a child, where family costs and consequences due to a child's illness or disabilities are derived from all family members and incorporated into the analysis. Future research is necessary to determine whether the

hypothesized inter-relationships among identified concepts are supported and/or validated by existing empirical support, and where empirical support/validation is still required. This would require an extensive literature search in the each of the concepts and inter-relationships among them, which is beyond the objective of this study.

Some researchers have argued that incorporating family spillover effects in the economic evaluation may challenge equity because the inclusion of family spillover may make the treatment of people without a caregiver and family networks less “worthwhile” than those with a caregiver and family networks (Basu & Metlzer, 2005; Dixon & Round, 2019; Lin et al., 2019; McCabe, 2019; Eve Wittenberg et al., 2019). In principle, the magnitude of effects of a child's illness or disability on an individual family member may differ based on the number of family members in the family. The caregiving responsibilities are shared among the family members; therefore, assuming the volume of caregiving is a fixed amount, such as the number of medication infusions per day, a child's illness or disability has less effect on an individual family member with a larger family network (larger family size) than an individual with a smaller family network (smaller family size). For instance, the family cost and health spillover effects of a child's illness or disability would be more significant for mothers in single-parent families than for mothers in two-parent families (assuming that a second parent is emotionally and financially tied to a child and the mother and is equally responsible for the upbringing of the child). Whether the magnitude of family spillover effects on mothers in single-parent families would be identical to the sum of family spillover effects for mothers and a second parent in two-parent family’s needs empirical inquiries and deserve further research. Therefore, it may not be entirely true that incorporating family spillover effects in the economic evaluation favors an individual with a caregiver (carer) and larger family networks compared to without. Moreover, a fundamental principle of economic evaluation is that meaningful conclusions depend on the intervention being compared to the best-available comparator intervention (Drummond et al., 2015). Decision makers' primary interest is comparative healthcare interventions' incremental costs and effectiveness. To get unbiased estimates of incremental costs and effectiveness, the patients receiving the alternative programs or interventions need to have similar characteristics, including family characteristics (the number of family members in the family). This could be achieved through randomized study design to address the equity concerns.

Another equity concern raised regarding incorporating spillover effects is that the inclusion of spillover effects in an economic evaluation will potentially draw resources towards treating illness of caregivers or family members. Thus, prioritize caregivers' or family members' health over patients' health. Accounting for the spillover effects may support maximizing the aggregate health of the population but not maximizing the patient health and may reduce the health of the patient (Basu & Metlzer, 2005; Dixon & Round, 2019; McCabe, 2019; Tubeuf et al., 2019) (Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). For instance, in a case of a CUAs, there might be a case where an intervention would be cost-effective when only the patient's (a child's) QALYs are considered but is not cost-effective when the family members' QALYs are included. Consider the following example. A child with chronic illness receiving informal care develops a life-threatening health condition. A new treatment is available, which would extend the patient's life but with the consequence of severe disability and required lifetime care from parents. The new intervention likely would increase the spillover effects for the parents (caregiver(s)) assuming that health spillover effects related to coping with death only lasts for a few years. Including both an increase in QALYs for the child and a decrease in QALYs in parents may reduce the aggregate QALY, and therefore, the results may not support providing care to the child with chronic illness. Alternatively, there might be a case where an intervention would be cost-effective when spillover effects are included but not cost-effective when only patient outcomes are considered. For instance, in a private payer healthcare system, early discharge from the hospital to the home could be more favorable when parent productivity costs associated with paid and/or unpaid work are included in the analysis because productivity loss avoids expensive hospital costs for parents. These examples are conceptualized to illustrate the points and requires empirical analyses.

To address this issue of equity in economic evaluation, such as a CUA, some researchers proposed including the health spillover effects on parents only if the QALY gain for the patient is positive or equal to zero (Tubeuf et al., 2019). Other researchers have proposed presenting the outcomes and costs for caregivers or family members alongside patient outcomes and in aggregate form within the CUA. For instance, presenting QALY gains or losses and changes productivity costs from the treatment separately and combined for the index patients, caregivers and/or family members (Cernat et al., 2021). Similar approaches could be taken while

conducting an economic evaluation from a family perspective. Another approach could be presenting two ICERs for a given intervention, one without family spillover effects and one with family spillover effects. Measurement equity issues are significant, and these issues need to be further discussed and investigated.

Conducting an economic evaluation from a family perspective may prioritize caregivers' or family members' health over the patient's health and have distributional consequences. However, excluding spillover effects on caregivers and family members is also inequitable (Brouwer, 2019). The family members sacrifice time and their health and well-being to provide care for the patient. Ignoring effects on family members in economic evaluation could lead to adverse effects on health and well-being of caregivers or family members and could results in policy decisions that disregard the health and well-being of caregivers and families. Moreover, one could argue that even if the new treatment does not improve the patient's health. Allocating the resources to the new intervention that improves the health and well-being of caregivers and family members will eventually benefit patients because caregivers and family members can provide better care.

The proposed theoretical framework showed how the spillover effects on family members could be incorporated into pediatric CUAs. However, there are many complex conceptual and practical challenges in pediatric economic evaluation, such as bereavment and other spillover effects when a patient dies, spillover effects outside the family members, and establishing a time horizon) that need to be addressed in future work.

3.4.2.1 Conducting a Pediatric Cost-utility Analysis from a Family Perspective

The systematic review of CUAs in Chapter 2 found that a small proportion of QALY-based pediatric CUAs included family health spillover effects in their analysis. Even within this small number of pediatric CUAs, there was heterogeneity in the methods or approaches employed to measure and incorporate the family health spillover effects. More importantly, only one study explicitly used theory and/or a theoretical framework to justify the methods used to incorporate the health spillover effects on caregivers and/or parents. Chapter 4 proposed a model for conducting a pediatric cost-utility analysis from a family perspective drawing on the concepts

from the proposed theoretical framework. The presented approach for 'conducting a pediatric cost-utility analysis from a family perspective' requires the family as a unit of analysis, where the total costs due to the child's illness and QALY are estimated from all the family members and included in the analysis. The total costs of a child's illness or disability from a family perspective would be estimated by summing the costs for all family members due to a child's illness or disabilities and the costs of the child's medical or/and non-medical resource use and the current and future opportunity cost of a child's productive time. This proposed method is referred to as an *isolated method* for incorporating family cost spillover effects in pediatric CUA because the family cost spillover effects on family members is estimated as an isolated quantity and summed with the costs of the child' medical or/and non-medical resource use and the current and future opportunity cost of a child's productive time. Similarly, from a family perspective, the total family QALYs can be estimated by summing the QALY from all family members, including a child with chronic illness or disability. This proposed approach of incorporating the family spillover effects is referred to as an *inherent method* for incorporating family health spillover effects in pediatric CUA because the health utility of each family member (family members' current health state) is measured independently, and therein, family health spillover effects (the caring for or caring about component of having an ill child). These health utility scores are used to estimate independent QALY for each family member. Finally, individual QALYs of family members are sum with the QALY of the index child to estimate the Family QALYs. This is currently the most common approach of incorporating caregiver effects in pediatric and maternal-perinatal CUAs observed in practice (Chapter 2).

The equity issues described earlier in the proposed theoretical framework are relevant to the proposed model. The subsequent paragraphs discussed key methodological challenges that need to be considered in adopting the proposed model for empirical analyses. There are primarily three challenges that necessitate caution when measuring effects on caregivers and incorporating these effects in the analysis. They are (1) identifying family members, (2) measuring family health spillover effects, and (3) double-counting of spillover effects. Before measuring any effects on family members, the family members must be identified. For the purpose of developing this theoretical framework, *the family* is theoretically defined as persons living in the same dwelling who are related to a child (≤18 years) with chronic illness or disability by blood,

adoption, or foster care and who are closely involved in the day-to-day operations of the household and who support other family members. Nonetheless, a family member may live away from home, but he/she is emotionally and financially tied to a child with chronic illness or disability and the family. It might not be feasible to include family health spillover effects for all family members in pediatric CUAs.

Second, the CUA is the recommended type of economic evaluation. Therefore, the child's and family members' health outcomes should be measured in QALYs. There are many challenges in deriving QALY for the pediatric population. Many preference-based instruments currently used in the pediatric population are instruments developed for adult populations and not designed for children (Kwon et al., 2018; Lamsal et al., 2020; Rowen, Rivero-Arias, Devlin, & Ratcliffe, 2020). The reliability and validity of these preference-based instruments such as EQ-5D, EQ-5D-5L, HUI-2, and HUI-3 in children are unknown (Kwon et al., 2018; Lamsal et al., 2020). Although pediatric preference-based measures are increasingly available such as Child Health Utility instrument (CHU9D) and child-friendly EQ-5D version (EQ-5D-Y), they cannot be used in children under six years of age (Stevens, 2009; Wille et al., 2010). In many cases, proxies such as parents, caregivers and healthcare professionals are used to elicit health utility scores in very young children or children unable to respond on their own. Proxy reporters can be effective for visible signs and symptoms but are less accurate for subjective HRQoL emotion, and utility measures (Baca et al., 2010; Pickard & Knight, 2005).

Furthermore, the most common approach for measuring family health spillover effects for CUAs is using indirect preference-based instruments, such as EQ-5D, EQ-5D-5L, HUI-2, and HUI-3 (Chapter, 2). These instruments were designed to measure the HRQoL of patients, and the domains included in these instruments may not adequately capture the effects of a child's illness or disability on family members or caregivers or may not be sufficiently sensitive to detect spillover effects. Direct elicitation methods such as the time-trade-off, standard gamble and visual analog scale may provide more flexibility in capturing family health spillover effects in HRQoL as they are not elicited based on specific domains. While direct elicitation methods may overcome the drawbacks of indirect methods, researchers have pointed out several challenges that need to be considered when using direct elicitation methods to measure family health spillover effects. For parents, it may be difficult to distinguish their own wellbeing and their

child's wellbeing when answering direct elicitation questions, such as the time they would be willing to trade-off to improve the child's health (Lavelle et al., 2019; Wittenberg & Prosser, 2013). These issues are discussed in detail in chapter 2. Furthermore, for the purpose of estimating the family QALY in present theoretical framework, we assumed that health utilities and QALYs generated from two different generic preference-based HRQoL instruments, CHU-9D and HUI-2, are of the exact nature and meaning and could be combined. However, these two preference-based HRQoL instruments differ in descriptive content and valuation techniques (Horsman et al., 2003; Stevens, 2009).

Finally, incorporating family health and cost spillover effects in pediatric CUAs may lead to the potential double-counting of the time costs of providing informal care and the parent's improved health benefit (Bobinac, Van Exel, et al., 2010; Koopmanschap, van Exel, van den Berg, & Brouwer, 2008; Wittenberg & Prosser, 2013). Double counting of family cost spillover effects occurs when the productivity loss of family members such as parents due to a child's illness or disability is included in both the cost (numerator) and the outcomes (denominator) of the incremental cost-effectiveness ratio (ICER) (Grosse et al., 2019). Parents who are caregivers may consider time sacrifices due to a child's illness or disability when expressing changes in their HRQoL due to a child's illness or disability. In other words, when parents value health states using the current indirect preference-based-HRQoL instrument such as EQ-5D or direct election methods, they may consider the effect of a child's health or disability on their own health on their ability to work and hence their subsequent income (Grosse et al., 2019; Tilling, Krol, Tsuchiya, Brazier, & Brouwer, 2010; Eve Wittenberg et al., 2019).

Researchers have proposed methods to avoid or minimize the double-counting of productivity costs. Hoefman and colleagues proposed a method for obtaining 'pure time cost' of caregiving hours via conjoint analysis with a discrete choice experiment that adjusts for the health effects of caregiving on caregivers (Hoefman, van Exel, & Brouwer, 2013). This avoids double-counting the caregiving time, which thus allows both time costs and health effects to be included in the CUA. Another option could be conducting sensitivity analyses without productivity costs (Tilling et al., 2010). This allows examining the influence of the productivity costs on results. Moreover, in the case of young children and children unable to respond independently, proxy reporters such as parents or caregivers are used to elicit the health utility scores. It may be

difficult for the caregiver or family members to separate their health from their child's health. Therefore, they might consider their own health while answering the HRQoL for the child leading to double counting of the disutility of their own health effects (Grosse et al., 2019; Eve Wittenberg et al., 2019; Wittenberg & Prosser, 2013). Although some researchers and the Second US Panel on Cost Effectiveness in Health and Medicine raised the issue of double counting of productivity costs this argument is not well articulated or empirically proven in literature and deserve more research. Until more conclusive evidence is available in this area, researchers who plan to conduct an economic evaluation of pediatric intervention from a family perspective should choose method minimize double counting of caregiving effects or family spillover effects.

3.4.3 Limitations

The terminology used to define theories, conceptual frameworks, and models for the purpose of literature searching varies within and across the disciplines. Therefore, the primary limitation of this study is that the search strategy may not have fully covered the diverse terminology used to refer to theories, conceptual frameworks, and models. However, the first author consulted with a librarian to ensure that the search strategy was as inclusive as possible. Secondly, some of the included theories like ecological systems theory, economic theories of fertility and the demand for children, and the transaction model have been continuously updated by the original authors. It is possible that some new concepts added to these theories were missed; however, core concepts remain the same. Finally, this review did not include studies published in languages other than English. It is possible that some non-English published studies were missed.

3.4.4 Implications for Future Research

Overall, the theoretical framework, ‘conducting pediatric economic evaluation from a family perspective.’ developed here is a first attempt to understand child health and development within a family context to incorporate family spillover effects in pediatric economic evaluation. First, theories, conceptual frameworks and models identified in this study provide a better understanding of child health and development in the context of pediatric economic evaluation. It may encourage future researchers to develop methods or approaches, such as an approach developed in this chapter, to consider family spillover effects while conducting an economic

evaluation of the pediatric intervention. Second, although there are several challenges, as highlighted above, in adopting the proposed approach ‘conducting a cost-utility analysis from a family perspective,’ for empirical analysis, this model can be used by researchers to incorporate family spillover effects or further develop empirical methods for including family spillover effects in the economic evaluation of child health interventions. Third, this study can be seen to advance the theoretical and conceptual conversations regarding the inclusion of family spillovers in pediatric economic evaluation. As noted by previous studies, current existing theoretical and conceptual frameworks are not well delineated (Prosser et al., 2007b; Prosser & Wittenberg, 2019b; J.M. Tilford & N. Payakachat, 2015; Ungar, 2011). Finally, this might encourage regulatory HTA agencies worldwide to make an explicit requirement for agencies to include both family cost and health spillovers in reports they need to submit for drug approval and reimbursement. Finally, the proposed theoretical framework ‘conducting a pediatric economic evaluation from a family perspective,’ which incorporates family spillover effects, can improve the quality of available evidence for funding and implementation of treatment and services that optimize the health and well-being of children and their families.

3.4.5 Conclusion

The insights that emerged from identified theories, conceptual frameworks, and models lead to the development of five concepts: health and well-being of family members is inter-dependent, collective family costs, maximizing health and well-being, family as a unit of analysis, and factors influencing child health and development. Integrating these concepts resulted in the theoretical framework conducting economic evaluation from a family perspective, which requires the family as a unit of analysis. Family costs and consequences of a child's illness are measured from all the family members and incorporated in the analysis. Based on the theoretical framework, an approach was proposed for incorporating family cost spillover effects using an isolated approach and family health spillover effects inherent approach. An isolated method requires estimating the cost for family members due to a child's illness and summing up the child's costs to include in the analysis to estimate the family costs. The inherent method requires calculating each family member's health utility, estimating QALYs independently, and then summing the QALYs of each family member to estimate the family QALYs. Future research

should explore other potential empirical methods to incorporate family spillover effects in pediatric economic evaluation using the family perspective.

Figure 3-4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

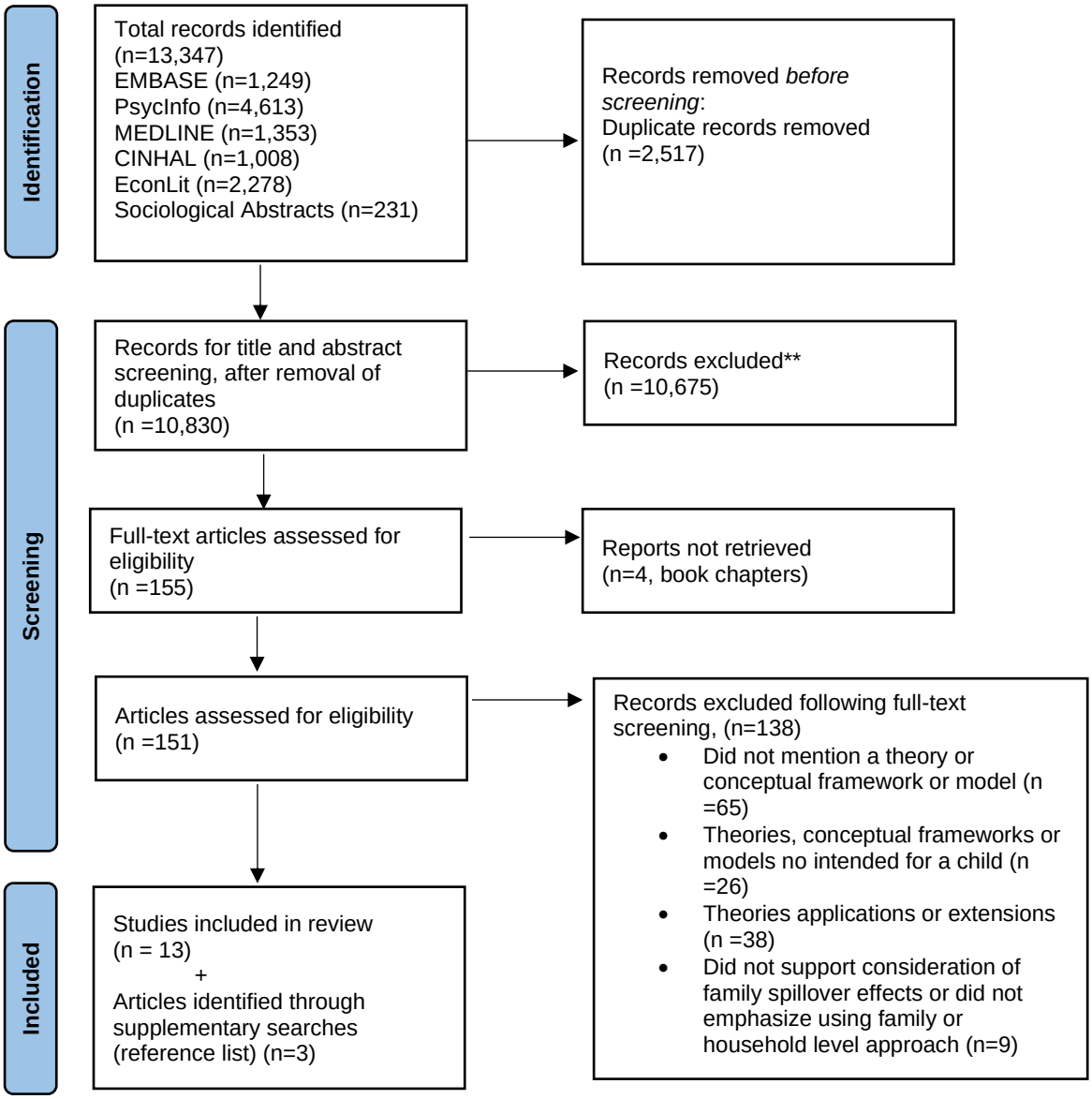


Table 3-1 Critical Appraisal Questionnaires for Theory, Framework and Conceptual Model

Critical appraisal questionnaires for theory, framework, and conceptual model

Reviewer:…… Date:……

Author(s):…… Name of theory, framework or conceptual model:…….

	Yes	No	Not clear	N/A
1. Do authors clearly state how the theory, framework or conceptual model was developed?	◻	◻	◻	◻
2. Are concepts, constructs or variables proposed in the theory, framework, or conceptual model logically related?	◻	◻	◻	◻
3. Are theoretical claims or propositions tested empirically?	◻	◻	◻	◻
4. Has the proposed theory, framework or conceptual model been validated in the used in the field?	◻	◻		

Note: Each criterion can receive a score of 0 to 1 ('yes'=1 and 'no' or unclear,' and 'not applicable=0).

Table 3-2 Study Characteristics

Author(s), year of publications	Type of publication	Name of a theory or a conceptual framework or model	Type of a theory or a conceptual framework or model	Discipline
Anderson et al., 2007	Peer-reviewed journal article	Anderson model on costs of caring for a child with a disability	Original	Health Service Research
Annett, 2001	Peer-reviewed journal article	A psychological model of children's health status in paediatric asthma	An extension of a psychological model of children's health (Bonner & Finney, 1996)	Health Service Research
Apps & Rees, 2001	Peer-reviewed journal article	Household production, full consumption, and the costs of children	An extension of Becker's model of household production (Becker, 1981)	Economics
Becker, 2009	Book chapter	The economics theory of fertility and the demand for children	Original	Economics
Berman et al., 1994	Peer-reviewed journal article	The household production of health	Original	Social Science
Bowen, 1966	Peer-reviewed journal article	The family systems theory	Original	Psychology
Bronfenbrenner, 1977, 1986)	Peer-reviewed journal article	Ecological systems theory	Original	Psychology

Bowlby & Ainsworth, 2013	Book chapter and peer-reviewed journal article	Attachment theory	Original	Psychology
Christensen, 2004	Peer-reviewed journal article	The health-promoting family	Original	Health Service Research
Fosco & Grych, 2013	Peer-reviewed journal article	A family systems model comparison	Application of family systems theory (Bowen, 1966)	Health Service Research
Golan & Weizman, 2001)	Peer-reviewed journal article	Familial approach to the treatment of childhood obesity: conceptual model	Original	Health Service Research
Jacobson, 2000	Peer-reviewed journal article	The family as a producer of health	An extension of the Grossman model (Grossman, 1972)	Economics
Lynch & Morley, 1995	Peer-reviewed journal article	Adaption to paediatric physical disability within the family system	Application of family systems theory (Bowen, 1966)	Psychology
McConkie-Rosell & Spiridigliozzi, 2004	Peer-reviewed journal article	A conceptual framework for genetic testing in Children	Application of family-focused framework, family system theory and family stress theory (Bowen, 1966)	Health Service Research
A. Sameroff, 2009; A. J. Sameroff, 1975; A. J. Sameroff & Chandler, 1975	Book chapters	The transactional model	Original	Psychology

Justice, 1999; Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012	Peer-reviewed journal article and book chapter	Sociocultural theory	Original	Psychology

Table 3-3 Summary of Included Theories, Conceptual Frameworks, or Models

Reference, year of publication	Name of a theory or conceptual framework or model	Summary of theory, conceptual framework, or model	Context for theory, conceptual framework, or model	Groups
Anderson et al., 2007	Anderson model on costs of caring for a child with a disability	• Family time, family income, goods and services consumed by family, and disability characteristics such as severity, functional limitations, aptitudes, constitute the framework for full burden of child disability.	• Disability policymaking based on public program data, that ignore costs to families of children with disabilities. • Incorporates costs of family caregiving time, productivity loss, leisure time, health outcomes of children with disability. • Develop evidence-based policy to alleviate burden of caring for families with children with disabilities.	•Considering family cost spillover effects in understanding the child development and health •Cost of rearing children

Annett, 2001	A Psychological Model of Children's Health Status in paediatric asthma	• The health outcomes and symptoms appraisal for children with the illness include the child's and parents' subjective and objective experiences. • An ineffective symptom appraisal in pediatric asthma can result in employment losses for parents, increased family stress, and increased use of health care services.	• Less attention has been given to measuring the quality of life than physiological data in children with illness. • The quality of life measure provides information on the child's and parents' subjective experience with the illness. • The quality of life measures helps to develop effective treatments.	•A family or household level approach in understanding the child health and development •Measuring health status of children
Apps & Rees, 2001	Household production, full consumption, and the costs of children	• The cost of rearing a child is the sum of consumption of market goods, domestically produced goods, and parental time in the form of childcare.	• The traditional approach to estimating the cost of raising children is narrow, only considers the costs of food, clothing, heat, and shelter. • The traditional approach ignores the costs associated with the re-allocation of parental time from market work and other household production activities such as sleep, leisure, and personal care to caring for children.	•Considering family cost spillover effects in understanding the child development and health •Cost of rearing children
Becker, 2009	Fertility, Household Production, and the Economics of the Family	• The expenditures on children by parents are a function of household income and preferences of parents, the number of children and the cost of child quality.	• Earlier household production models focused on the effects of marriage and family and raising own children considering the division of labour within households.	•A family or household level approach in understanding child health and development •Considering family cost and health spillover effects in

		• The well-being of children depends on expenditures, the reputation and contacts of their family, their endowments of genes and culture.	• The theory of fertility answers the following questions why rural fertility had traditionally exceeded urban fertility, why a rise in the wage rate of working women reduces their fertility and why families with higher incomes have had more children.	understanding the child development and health •Cost of rearing children
Berman et al., 1994	The household production of health	• The household production of health is a dynamic process through which households combine their knowledge, resources and technologies, services, information, and skills to restore, maintain, and promote their members' health.	• Efforts to control disease and improve health in developing countries require collaboration between different disciplines. • Public health in developing countries could be enhanced by a holistic understanding of the household's health improvement role.	•A family or household level approach in providing care for the child •Child health and development
Bowen, 1966	The family system theory	• The family is one emotional system or unit wherein each member intensely influences other family members' thoughts, feelings, and actions. • Family members seek each other's attention, approval and support and react to each other's needs, expectations, and upsets. • Changes in one family member's emotional functioning unit are predictably and automatically	• To facilitate efforts of family members to gain the tools to deal with emotional processes within oneself and family when confronted with anxiety-provoking life situations and events.	•A family or household level approach in providing care for the child •Providing care for children with disabilities or illness

		compensated for by changes in the emotional functioning of other members of that family. • The family collectively seeks ways to reduce tension and maintain stability.		
Bronfenbrenner, 1977, 1986	The ecological systems theory	• A child being at the center of four ecological levels (microsystem, mesosystem, ecosystems and macrosystems) that nested within each other. • The microsystem refers to the relationships and interactions children have with their immediate surroundings, such as family or caregivers, school, neighbourhood, and daycare, directly impact their development. • The relationships in this system are bi-directional, meaning that children can be influenced by the behaviour and belief of the parents and are capable of changing the behaviour and belief of the parents.	• Describes how children's inherent qualities and environments interact to influence how they grow and develop.	•A family or household level approach in understanding child health and development •Child health and development
Bowlby & Ainsworth, 2013	Theory of attachment	• Children develop attachment behaviours such as crying, smiling and other	• Understand the separation anxiety and distress children	•A family or household level approach in

		facial emotional expressions to maintain proximity to the caregiver. • The relationship between caregiver and infant is dynamic, in that the infant's response shapes the mother's response and successively shapes that of the child. • The earliest bonds formed by the child and their caregivers have tremendous impacts health and well-being of the child and continue throughout life.	experience when separated from their primary caregivers. • Understand how children develop earliest bonds with caregivers.	understanding the child health and development •Providing care for children with disabilities or illness
Christensen, 2004	The health-promoting family	• The societal factors (income, wealth, education, time, and family structure) and community factors (community, school, health services, peer groups and daycare) work along with processes internal to the family (family's ecocultural pathway, genetics/ family health history, health practices) to produce individual and collective actions the form of family health practises to promote children's health, well-being, and development.	• Understand how family members actively promote, develop, and sustain their own (including children) and other family members' health and well-being in their everyday lives.	•A family or household level approach in providing care for the child •Providing care for children with disabilities or illness

		• Health practices of the family are determined through the norms, values, and goals of the family.		
Fosco & Grych, 2013	Unique predictors, interparental indirect effects and family as a context model	• Parents (father and mother), family positivity, family negativity, and interparental conflict predict the children's emotion regulation. • Interparental conflict interacts with family-level and parent-child dynamics to impact children's emotion regulation. • Parents constitute the earliest and most influential interpersonal context of children's emotional regulation but are shaped by the quality of marital and family-wide functioning beyond what is explained in parent-child relationships.	• The influence of family functioning on children's emotional regulations is studied separately. • Understand how the interplay of family processes, interparental and parenting dimensions within a broader family system affects children's emotional regulations.	•A family or household approach in understanding child health and development •Considering family health spillover effects in understanding the child development and health •Child health and development
Golan & Weizman, 2001	Familial approach to the treatment of childhood obesity: conceptual model	• The parent can be used as the agent of change by maintaining a healthy lifestyle in the family to prevent childhood obesity. • The home and family environment where children first acquire healthy eating habits.	• In the traditional approach to treating obesity in a child, the child is the primary agent to change and control his or her behaviour. • Delivering a change through parents, using a familial approach, is crucial for treating obesity.	•A family or household level approach in providing care for the child •Providing care for children with disabilities or illness

		• A child achieves a healthy weight status through parental cognitive and behavioural change (increasing healthy eating habits at home, exercising regularly, and promoting healthy habits in their children).		
Jacobson, 2000	The family as the producer of health	• A family makes investments in its children because children cannot independently make decisions about investment in their own health. • Each family member is the producer of his own health and the health of other family members, and that is not only his own income and wealth but also the earnings of other family members.	• Individuals as a producer of health in the original Grossman model. • Decisions to invest in children's health are made jointly within the family. • The individual's family situation needs to be considered when designing and evaluating prevention, treatment, rehabilitation, and educational health programmes.	•A family or household level approach in understanding child health and development •Considering family cost spillover effects in understanding the child development and health • Child health and development
Lynch & Morley, 1995	Adaption to paediatric physical disability within the family system	• Having a child with a physical or medical disability in a family impacts the well-being of the other family members and the family unit itself. • The child health intervention should be identified through the appraisal of family characteristics (the number of children, marital status, the	• Family counsellors use a family perspective system approach to counselling children with physical disability and their families. • Family counsellors need to understand the unique issues and needs present in families.	•A family or household level approach in providing care for the child •Providing care for children with disabilities or illness

		number of family members with chronic illness or disability), culture, belief system, function and roles of family members and interaction and communication between family members.		
McConkie-Rosell & Spiridigliozzi, 2004	A Conceptual Framework for Genetic Testing in Children	• Health professionals should consider a child a part of the family and adopt a family-centred approach when providing genetic counselling interventions or testing for children. • Explore the family's values and beliefs regarding genetic testing and coping behaviours. • Partner with parents to identify ways to promote healthy interaction of information into a child's self-concept and facilitate positive adaptation of the child to the genetic information family. • Parents are responsible for creating an environment that allows their children to grow, cope, and adjust to relevant genetic information as part of their roles in nurturing their children into social beings.	• The conventional approach to genetic testing for children emphasizes individual autonomy. • Ignores the family beliefs and values and parents' concern for their children. • The child is a part of the family.	•A family or household level approach in providing care for the child •Providing care for children with disabilities or illness

A. Sameroff, 2009; A. J. Sameroff, 1975; A. J. Sameroff & Chandler, 1975	The transactional model	• The child's neurological, psychological, and social development is a dynamic process resulting from complex and continuously changing interactions between the child and experiences provided by his or her social settings. • Parents and children are involved in many environmental settings that their participants are changing and being changed.	• Understand how nature and nurture interact in the development of positive and negative outcomes for children.	•A family or household level approach in understanding child health and development •Considering family health spillover effects in understanding the child development and health •Child health and development
Justice, 1999; Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012	Sociocultural theory	• The cognitive development in children, such as language, abilities, literacy, reasoning, problem solving and self-regulation, takes place in a social context through assistance provided by more experienced adults mainly, parents who act as intelligent guides. • Through the adults' mediated assistance or social	• Understand the role of parents in young children's learning and development.	•A family or household level approach in understanding child health and development •Child health and development

		guidance at a level beyond the children's independent capabilities, children gradually learn to function intellectually on their own.		

Table 3-4 Critical appraisal of included theories, theoretical frameworks, and models

Author(s), year of publications	Do authors clearly state how the theory, framework or conceptual model was developed?	Are concepts, constructs or variables proposed in the theory, framework, or conceptual model logically related?	Are theoretical claims or propositions tested empirically?	Has the proposed theory, framework, or conceptual model been validated in the used in the field?	Total score
Anderson, Dumont, Jacobs, & Azzaria, 2007	Yes	Yes	Yes	Yes	4
Annett, 2001	Yes	Yes	Not clear	Yes	3
Apps & Rees, 2001	Yes	Yes	Yes	Yes	3
Becker, 2009	Yes	Yes	Yes	Yes	4
Berman, Kendall, & Bhattacharyya, 1994	No	Yes	Yes	Not clear	3
Bowen, 1966	Yes	Yes	Not clear	Not clear	2
Bronfenbrenner, 1977, 1986	Yes	Yes	Yes	Yes	4
Bowlby & Ainsworth, 2013	Yes	Yes	Not clear	Not clear	2
Christensen, 2004	No	Yes	Not clear	Yes	3
Fosco & Grych, 2013	No	Yes	Yes	Not clear	3
Golan & Weizman, 2001	Yes	Yes	Yes	Not clear	3
Jacobson, 2000	Yes	Yes	Not clear	Yes	3
Lynch & Morley, 1995	No	Yes	Not clear	Not clear	1
McConkie-Rosell & Spiridigliozzi, 2004	Yes	Yes	Not clear	Not clear	2
A. Sameroff, 2009; A. J. Sameroff, 1975; A. J. Sameroff & Chandler, 1975	Yes	Yes	Not clear	Not clear	2

Justice, 1999; Lev Semenovich Vygotsky, 1980; Lev S Vygotsky, 2012	Yes	Yes	Not clear	Not clear	2

Table 3-5 Mapping of Synthesized Constructs and Concepts for Conducting an Economic Evaluation from a Family Perspective

Synthesized constructs	Concepts	Synthesising argument
•Bidirectional relationship between the child development and family •Complex relationships between child development and his/her family •A dynamic relationship between a child's and family members' health and well-being •Interdependent utilities •Genetic factors •Changing roles of family members	Health and well-being of family members is inter-dependent	Conducting pediatric economic evaluation from a family perspective requires the family as the unit of analysis to evaluate the child's health and economic and/or well-being where family costs and consequences related to a child's illness or disability are derived from all family members and incorporated into the analysis. This is because child's, parents' and other family members' health and wellbeing are interdependent, they collectively incur costs and allocate resources and are influenced by family's socio-economic status, cultural and religious beliefs along with environmental and societal factors.
•Parent cost •A dynamic relationship between family's cost and child health and well-being •Intra-family resource allocation	Collective family costs	
•Family health maximization •Family utility maximization •Altruism of parents towards their own children	Maximizing family health and well-being	
•A family is a producer of health •A family is a system •Family decision making •A family-centred approach	Family is a unit of analysis	
•Family's socioeconomic status •Family's' cultural and religious beliefs •Environmental and societal factors	Factors influencing child health and development	

Table 3-6 Mapping of Codes and Synthesized Constructs Included within the Concept Health and Well-being of Family Members is Inter-dependent

References	Codes	Synthesized constructs	Concept
Bowlby & Ainsworth, 2013	Parent's treatment of a child is a key to his/her development	Bidirectional relationship between the child development and the family	Health and well-being of family members is interdependent
Bronfenbrenner, 1986; Sameroff & Chandler, 1975	Bi-directional effects		
Bowlby & Ainsworth, 2013; Bretherton, 1992	Interacting to influence each (child and parent) other's behaviour		
Sameroff, 1975	The reciprocal influence of the child's behaviour on parents' behaviour		
Bowlby & Ainsworth, 2013	The pattern of attachment is influenced by ways parents treat their children		
Vygotsky, 1988; Vygotsky, 2012	Parental roles in shaping children's learning and development		
Sameroff, 2009	Child development and the family relationship changes over time	Complex and changing dependency relationships between child development and his/her family	
Bowen, 1966; Annett, 2001	Changes in the child's health directly impact the family member's health and well-being	A dynamic relationship between a child's and family members' health and well-being	
Bowen, 1966	Mother and father-child subsystems are central factors for children's emotional regulation		
Fosco & Grych, 2013)	Parental conflict influences children's emotion regulation		

Lynch & Morley, 1995; Bowen, 1966	All family members are affected by the actions of anyone member		
Lynch & Morley, 1995	Diagnosis of disability or disease of a child influence the health and well-being of family members		
Bowen, 1966; Brown, 1999	Relationship between the magnitude of effects and strength of the relationship		
Annett, 2001	Ineffective parents' interpretation of a child's symptoms increases family stress		
Becker, 2009	Parent utility depends on children utility	Interdependent utilities	
Jacobson, 2000	Each family member produces utility of other members		
Jacobson, 2000; Grossman, 1972	Children's health and intelligence depends on genetic inheritance	Genetic factors	
Becker, 2009	Parents prefer biological children because of less uncertainty		
Christensen, 2004; (McConkie-Rosell & Spiridigliozzi, 2004)	Examining the family history of illness and genetics in understanding the health and well-being of a child		
McConkie-Rosell & Spiridigliozzi, 2004	A genetic diagnosis is a family identity		
Lynch & Morley, 1995	Changing career choice, recreation,		

	and social activities of parents	Changing roles of family members	
Bowen, 1966	Compensating dysfunction of the other family member who is ill		
Lynch & Morley, 1995	Diagnosis of disability alter the family's lifestyle and future goals		

Table 3-7 Mapping of Codes and Synthesized Constructs Included within the Concept of a Collective Family Costs

References	Codes	Synthesized constructs	Concept
Apps & Rees, 2001; Becker, 1981, 2009; Jacobson, 2000; Anderson et al., 2007; Lynch & Morley, 1995	Costs incurred by parents	Parent cost	Collective family costs
Apps & Rees, 2001; Becker, 1981, 2009; Jacobson, 2000	Cost of a child is the sum of consumption of market goods and services, and parental time		
Anderson et al., 2007	Relationship between child's severity of disability or diseases and parents' employment time		
Anderson et al., 2007; Apps & Rees, 2001	Collective approach in determining the full burden of illness of a child		
Jacobson, 2000; Anderson et al., 2007	Increased a child's health capital increase the parental employment	A dynamic relationship between family's cost and child health and well-being	
Anderson et al., 2007	Improved child health frees up time for economic activities for parents		
Anderson et al., 2007; Lynch & Morley, 1995	Parental employment influences the needs of the child with a disability or disease		
Berman et al., 1994	Combining social, economic and health inputs to restore, maintain, and promote the child's health	Intra-family resource allocation	
Apps & Rees, 2001; Jacobson, 2000	Decisions to invest in a child's care based on family income,		

	savings, and consumption of everyday goods and services		

Table 3-8 Mapping of Codes and Synthesized Constructs Included within the Maximizing Family Health and Well-being

References	Codes	Synthesized constructs	Concept
Berman et al., 1994	Family combines social, economic and health inputs to restore, maintain, and promote the family health	Family health maximization	Maximizing family health and well-being
Bowen, 1966	The family act as an emotional unit reduces family tension and maintain stability		
Apps & Rees, 2001; Becker, 1981, 2009; Jacobson, 2000	Making consumption decisions to maximize the family utility	Family utility maximization	
Becker, 2009	Parents have concern for the well-being of their own child	The altruism of parents towards their children	
Bowen, 1966	Each family member devotes a certain amount of self-being to the welfare and well-being of others		

Table 3-9 Mapping of Codes and Synthesized Constructs Included within Family is a Unit of Analysis

References	Codes	Synthesized constructs	Concept
Jacobson, 2000; Berman et al., 1994)	Family is a producer of health	A family is a producer of health	Family is unit of analysis
Jacobson, 2000	Each family member is the producer of his own health and the health of other family members		
(Berman et al., 1994	Household know how to produce healthy children		
(Bowen, 1966; Lynch & Morley, 1995)	Changes in one part of the system make changes in other parts of the system	A family is a system	
(Bowen, 1966; Bowen, 1978. Bronfenbrenner, 1977, 1986)	Considering family as a whole and what they do		
(Lynch & Morley, 1995)	The actions of one member affect all family members		
(Christensen, 2004)	Family as a system that works to promote children's health and well-being and development		
(Jacobson, 2000; Berman et al., 1994; Bowen, 1966)	Deciding on inputs to restore, maintain and promote the health and well-being	Family decision making	
(Jacobson, 2000)	The family decides to invest in child health		
(Golan & Weizman, 2001)	The parent as authoritative and role model		
(Annett, 2001)	Including perceptions of both parent and children health outcome assessment for children	A family-centred approach	

	Considering all the family members within a family		
McConkie-Rosell & Spiridigliozzi, 2004; Golan & Weizman, 2001)	Family-based intervention		
(Golan & Weizman, 2001)	Implementing intervention and treatment focused on the entire family		
(McConkie-Rosell & Spiridigliozzi, 2004)	Joint counselling		

Table 3-10 Mapping of Codes and Synthesized Constructs Included within the Concept Factors Influencing Child Health and Development

References	Codes	Synthesized constructs	Concept
Bronfenbrenner, 1986; Anderson et al., 2007	Family income affects the child health and development	Family socioeconomic characteristics	Factors influencing child health and development
Becker, 2009	The demand for children depends on family income		
Lynch & Morley, 1995; McConkie-Rosell & Spiridigliozzi, 2004)	Considering family culture, belief system and interactions while designing interventions or treatments	Family culture and religious characteristics	
Christensen, 2004	Mother's health status, belief, behaviour, and practices impact child health		
Golan & Weizman, 2001	Family health, belief, and culture influence the child health		
Sameroff, 1975, 2009; Sameroff & Chandler, 1975; Bronfenbrenner, 1986	Child development and health is influenced by the multiple social and environmental contexts and their interactions in which a child lives	Environmental and societal characteristics	
Bronfenbrenner, 977; 198:	Reciprocal interchanges between the child and family's health and well-being and environment		

Table 3-11 Costs Included in Public Healthcare Payer, Family, and Societal Perspectives for Pediatric Economic Evaluation

			Perspective		
			Public Health Care Payer	**Family Payer**	**Societal Payer**
Resource consumed	**Cost elements**	**Examples**			
Costs of resources consumed by children	Direct health care costs covered by the public payer	• Drugs, medical devices, procedures • Healthcare providers • Hospital services • Diagnostic, investigational, and screening services • Rehabilitation	Yes	No	Yes
	Direct healthcare costs covered by the private payer (falling outside of public payer)	• Drugs, medical devices, procedures (not covered by public payer) • Rehabilitation (not covered by public payer) • Special equipment(s) (not covered by public payer)	No	No	Yes
	Direct non-health care costs covered by the public payer	• Education-based services and supports • Community-based social services, such as social support programs • Behavioral support and educational support programs • Disability support programs, such as government tax deductions and subsidies.	No	No	Yes

	Out-of-pocket expenses	• Out-of-pocket costs or co-payments for medical or non-medical service for the child's health (e.g., copayments for drugs or special equipment) • Out-of-pocket costs for family members of transportation and lodging for the child to receive medical or non-medical services	No	Yes	Yes
	Other household expenditures	• Household expenses related to child's illness or disability (home modifications: stairs indoors and outdoors, changes to the bathroom, upgrading bathrooms and others)	No	Yes	Yes
	Productivity costs	• Lost time from schoolwork • Lost of productivity (time) from paid and unpaid work that occurs in adult years	No	Yes	Yes
Costs of resources consumed by family members due to a child's illness	Direct health care costs covered by the public payer	• Drugs, medical devices, procedures • Healthcare providers • Hospital services • Diagnostic, investigational, and screening services • Rehabilitation	Yes	No	Yes
	Direct healthcare costs covered by the private payer (falling outside of public payer)	• Drugs, medical devices, procedures (not covered by public payer) • Rehabilitation (not covered by public payer)	No	No	Yes

	Direct non-health care costs covered by the public payer	• Community-based social services, such as social support programs	No	No	Yes
	Out-of-pocket expenses	• Out-of-pocket costs for family members of transportation and lodging for the child to receive medical or non-medical services • Out-of-pocket costs or co-payments of family members for their health and well-being as a direct result of caring for a child with chronic illness or disability • Out of pocket costs of family members for transportation and lodging for the family members to receive medical or non-medical services	No	Yes	Yes
	Productivity costs or production losses	• Lost productivity (time) of family members from paid and unpaid labor associated with treatment and care for child	No	Yes	Yes

4 Health-Related Quality of life and Mental Health Care Utilization in Parents of Children with Neuroinflammatory Disorders: A Cross-Sectional Study

4.1 Introduction

Paediatric neuroinflammatory disorders (ND), also referred to as neuroinflammatory diseases, encompass a broad range of conditions characterized by brain dysfunction due to an autoimmune process (Tardieu et al., 2016; Van Mater, 2014). Neuroinflammatory disorders occur when the immune system (cells that normally fight infection) attacks the tissues in the brain and spinal cord. The signs and symptoms of ND are heterogeneous depending on the type of ND, but, generally, these conditions present acutely with one or more neurological symptoms, including cognitive and behavioural dysfunction, seizure, severe fatigue, or visual impairment (Amato et al., 2014; Khan, Pallant, Amatya, Young, & Gibson, 2011; Morales et al., 2000). The most common paediatric NDs are multiple sclerosis (MS), autoimmune encephalitis, optic neuritis, and transverse myelitis (Absoud et al., 2016; Longoni, Levy, & Yeh, 2016; Twilt & Benseler, 2013). Many cases of neuroinflammation in children occur only once in a lifetime (monophasic), while others may be recurrent: both situations can result in chronic disability with significant impacts on a child's independence and quality of life (Absoud et al., 2016; Liu et al., 2018). Children and adolescents with a ND such as MS have experienced greater emotional distress, decreased psychological functioning, and decreased school functioning compared to healthy children and adolescents (Amato, Krupp, Charvet, Penner, & Till, 2016; MacAllister, Boyd, Holland, Milazzo, & Krupp, 2007; Mikaeloff, Caridade, Billard, Bouyer, & Tardieu, 2010; Till et al., 2012).

Consequently, children with ND may require caregivers to support them in their everyday life, provided primarily by parents or other family members. The assistance provided by informal caregivers covers a wide range of activities, including personal care (bathing, feeding, and medical support), mobility, recreation and taking them for frequent medical checkups and treatments. Caring for children and/or adults with ND is known to influence parents' emotional and physical health as well as have an impact on household finances and engagement in paid

employment (Olivia Ernstsson et al., 2016; García-Domínguez et al., 2019; Ghai et al., 2021; Luca, Ortega-Castro, & Patti, 2021; Naci, Fleurence, Birt, & Duhig, 2010; O'Mahony et al., 2019; Paz-Zulueta, Parás-Bravo, Cantarero-Prieto, Blázquez-Fernández, & Oterino-Durán, 2020; Petrikis, Baldouma, Katsanos, Konitsiotis, & Giannopoulos, 2019). Feelings of guilt and anxiety coupled with concern about their children's future have been linked to increased adverse psychological effects on parents of children with ND (Ghai et al., 2021; D. Hinton & Kirk, 2015, 2017).

The psychological and emotional burdens experienced by parents can differ according to the stages of the disease. Parents may experience a higher burden at the time of initial diagnosis and during the process of adaptation to living with a child with a ND (Cross, Shanks, Duffy, & Rintell, 2019; Marrie et al., 2020). As the disease progresses, caregiving becomes physically and emotionally more demanding and time-consuming leading caregivers to neglect their own needs and care, hence, negatively impacting their quality of life and well-being. The diagnosis of MS during childhood has been associated with reduced parental health-related quality of life (HRQoL) and family functioning (O'Mahony et al., 2019).

Moreover, raising and caring for a child with ND can have a significant financial burden on families (Luca et al., 2021; Naci et al., 2010). The time required to care for children with ND combined with the high cost of specialized childcare may reduce parents' ability to sustain paid employment, resulting in substantial productivity losses for families. The productivity loss includes time losses incurred by parents and caregivers from both paid and unpaid labour for providing care to the child (Grosse et al., 2019) . The literature examining employment outcomes for families with a child with a chronic illness or disability indicates that parents are less likely to be employed and more likely to report employment problems such as quitting work, decreasing work hours, or changing jobs because of their child's condition (J. Hatzmann, N. Peek, H. Heymans, H. Maurice-Stam, & M. Grootenhuis, 2014; A. Kish et al., 2018).

Caregivers and/or parents may use mental health services and pay out-pocket to cope with mental health problems caused by high caregiving demand or higher levels of stress or psychological difficulties stemming from the disability of a child. A study comparing 156 mothers of children with MS (MS mothers) and 624 mothers of children without MS (non-MS

mothers) showed that had a higher prevalence of mood and anxiety disorders than non-MS mothers (Marrie et al., 2020). The same study revealed that MS mothers used more mental health services before and after their child's MS diagnosis than non-MS mothers (Marrie et al., 2020). The caregivers of adults with MS had more emergency department visits and hospitalizations than non-caregivers (Gupta, Goren, Phillips, & Stewart, 2012).

Research evaluating the effects of ND on the health and well-being of parents, caregivers and family members has grown in recent years. However, these studies are predominantly focused on caregivers of adults with ND. Of those focused on caregivers and/or parents of children with ND, most studied caregivers and/or parents of children with MS (Grima et al., 2000; Naci et al., 2010). Compared to other childhood illnesses or disabilities such as autism spectrum disorder, cerebral palsy and congenital anomaly, relatively few studies have measured the health-related quality of life, productivity losses and mental health service use by caregivers and parents of children with ND (Dudley & Emery, 2014; Kruse et al., 2009; Marrie et al., 2020; Reichman et al., 2008; Shahat & Greco, 2021; Eve Wittenberg et al., 2019). In health economics, the effects of pediatric chronic illness or disabilities on parents and/or caregivers and family are commonly known as *spillover effects* and can be categorized into *family costs* and *health* spillover effects (Chapter 1). The family cost spillover effects refer to the impact of illness or disability of a child on the economic well-being of family members, such as productivity costs of parents associated with time losses for paid labour and/or usual day-time activities due to a child's illness, direct and non-healthcare costs of parents due to a child's illness (Chapter 3). The family health spillover effects refer to the impact of a child's illness or disability on the health and well-being of family members, such increments, or decrements in parents' health utility due to a child's illness, changes in parents' health-related quality of life (HRQoL) due to a child's illness (Chapter 3). In summary, research has shown that having and caring for a child with ND could significantly impact the health and well-being and financial prosperity of parents and/or caregivers.

The original plan of this study was to measure family costs and health spillover effects in parents of children with cerebral palsy (CP) and multiple sclerosis (MS). I had planned to collect the data from two planned randomized control trials (CHILD-BRIGHT study 1.3 and SickKids Study on metformin with control groups). The objectives of the original study were to: (i) compare the

incremental cost of metformin + physiotherapy to standard care per QALY gained in CUAs estimated with and without the incorporation of health and costs spillover effects on the parents of children with cerebral palsy (CP) and to evaluate how the conclusion may change when the spillover effects were included in the CUA and (ii) compare the incremental cost of metformin to standard care per QALY gained in CUAs estimated with and without the incorporation of health and costs spillover effects on parents of children with MS and examine how the conclusion may change when the spillover effects were included in the CUA. The detail description on methods (data collection, costing, valuing outcomes, imputation of missing values, analysis and uncertainty analysis) can be found in Appendix Q. However, because of the COVID-19 pandemic, the data collection for both RCTs were suspended. Therefore, considering timelines for the completion of data collection and PhD, we had to re-design the data collection and this study's objectives to on the measurement of HRQoL, care-related quality of life and costs in parents and/or caregivers of children with ND without any control groups.

Measuring HRQoL, care-related quality of life and costs in parents and/or caregivers summarize experiences of parents and/or caregivers and therefore illustrate the burden of having and caregiving for a child with ND. More importantly, measuring HRQoL, care-related quality of life and costs in parents of ND is crucial to determining what services and supports parents and caregivers need to improve their own health and well-being. Minimizing the parent and/or caregiver burden could also improve the health outcome for the child with ND.

4.2 Study Objectives

There were two primary objectives for this study. The first aim was to measure the HRQoL and care-related quality of life of parents and/or caregivers of children with ND. The second aim was to measure the mental health care service utilization and costs for parents and/or caregivers of children with ND due to a child's illness. The costs for parents include out-of-pocket costs paid by parents for their mental health services to manage increased stress or pressure related to caregiving responsibilities and the productivity costs associated with parental time losses from paid labour and/or usual activities to provide care for the child with ND(s).

4.3 Methods

4.3.1 Study Design

This was a cross-sectional observational study. Ethics approval was obtained from the Hospital for Sick Children (SickKids; Toronto, Ontario, Canada) (Appendix C). The parents provided written informed consent, and the children provided assent.

4.3.2 Recruitment and Data Collection

Participants were enrolled through the Neuroinflammatory Disorders Clinic at the Hospital for Sick Children, Toronto, Canada. Children and their parents were invited to participate in the study during routine clinic visits. The inclusion criteria for children were: (1) aged between five to 18 years, (2) diagnosed with ND, and (3) able to understand English. The types of ND included multiple sclerosis (MS), monophasic acquired demyelinating syndrome (Mono-ADS), neuromyelitis Optica spectrum disorder (NMOSD), autoimmune encephalitis (AE), myelin oligodendrocyte glycoprotein (MOG-IgG)-recurrent disease, systematic, and central nervous system (CNS) inflammation and CNS inflammatory disease but diagnosis not known. The inclusion criteria for parents were: (1) parents of children aged five to 18 years, (2) parents of children diagnosed with ND, and (3) able to understand English. If children and their one parents (respondent parents) agreed to participate in the research, the researcher (RL) contacted parents and administered questionnaires by telephone.

Data were collected by telephone between October 2020 and January 2022. Parents were interviewed. The initial plan was to collect the data in in-person interviews. However, because of the COVID-19, researchers had to change to data collection method to telephone interviews. A twelve-month pre-COVID-19 recall period was used to eliminate the effects of the COVID-19 pandemic on parents' productivity losses from work and/or usual activities, and mental health services use due to a child's illness. For some of the respondent parents, the recall period was going to be more than two years. Furthermore, resource uses questionnaires were designed to measure the impacts of a child's illness on parents' productivity. For some respondent parents, it can be challenging to separate the time losses from their health or well-being or other's child's health, and well-being and mental health service uses due to their own illness or child's illness. The telephone-based interview would help answer their questions and help get accurate

estimates. Furthermore, usually interview-based surveys minimize the missing data. The data were collected using paper forms, entered in Redcap (Harris et al., 2009), and subsequently exported into R for analysis (R Core Team, 2013) by the researcher (RL). The interviewer-administered a sociodemographic questionnaire for parent and child (Appendix D), the Health Utilities Index (HUI) for the respondent parent and the child, (Horsman et al., 2003), and parents' productivity and mental health service use questionnaire, and the care-related quality of life instrument (CarerQol) (Brouwer et al., 2006b). Only one parent (the respondent parent) was interviewed. The questionnaires are appended in Appendix E to H. The disease diagnosis was obtained from the Neuroinflammatory Patient Registry. The Neuroinflammatory Patient Registry includes information on children with neuroinflammatory disorders. The purpose of the Registry is to collect data on children with ND for use in research and aims to increase the knowledge of childhood neuroinflammation and help doctors develop better ways to diagnose and treat children with ND.

4.3.3 Measures

4.3.3.1 Sociodemographic Variables

The respondent parent's current socio-demographic data were collected, including age in years, gender, sex, total annual household income, education, marital status, and current employment status. The respondent parent was also asked about his/her relationship with the child and his/her role in caregiving (primary, equal, or secondary caregiver). For the purpose of this study, the primary caregiver was defined as the person primarily responsible for the care and upbringing of a child with ND. Equal caregivers, for instance, a mother and father, were defined as two persons equally responsible for the care and upbringing of a child with ND. The secondary caregiver was defined as the second most responsible for the care and upbringing of a child with ND. Moreover, the respondent parents were asked about the child's demographic information, including age (month, year), sex, and gender.

4.3.3.2 Health Utilities Index (HUI)

The HUI is a generic preference-based multi-attribute comprehensive system for measuring health status and HRQoL (Horsman et al., 2003). HUI is a family of three distinct, stand-along measurement systems: Mark1 1 (HUI1), Mark 2(HUI2) and HUI Mark 3 (HUI3). HUI2 and

HUI2 are commonly used. HUI is currently defined as including both HUI2 and HUI3 systems. Therefore, current HUI questionnaires cover both systems. The utility scoring systems (or algorithms for converting responses into health attribute levels and single- & multi-attribute health utility scores) are different. Each HUI measurement system has four components: a health-status classification system, a preference-based scoring function, data collection questionnaires, and algorithms for converting responses into health attribute levels and single- & multi-attribute health utility scores. HUI has three standard assessment periods: past one week, past two weeks, and past four weeks. The past one-week recall period was used for this study (Appendices F & G). The HUI2 describes an individual's overall function based on seven attributes: sensation, mobility, emotion, cognition, self-care, pain, and fertility, with each attribute consisting of 3 to 5 levels. Fertility is not assessed when administering HUI in children and was not included in the HUI questionnaire for respondent parents (Horsman et al., 2003). The HUI3 describes an individual's overall function based on eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain, with each attribute consisting of 5 to 6 levels. An interview-administered parent-proxy assessed HUI (HUI123P4.EN40Q) was used for children with ND. An interview-administered self-assessed HUI (HUI123S4.EN40Q) was used for respondent parents. Both HUI2 and HUI3 have also been used in children over eight years and include a parent proxy for children aged six to eight years or children with cognitive and/or communication difficulties (Horsman et al., 2003; Kwon et al., 2022; Lamsal et al., 2020). The HUI3 has also been used to measure the health effects on family members of children or adults with a disability or chronic illness (Neumann et al., 1999; Payakachat, Tilford, Brouwer, van Exel, & Grosse, 2011; Eve Wittenberg et al., 2019). Compared to other preference-based instruments, such as the Short-Form Six-Dimension (SF-6D) and the Quality of Well-Being Scale-Self Administered (QWB-SA), the HUI has been shown to be more sensitive to predictors of depressive symptoms in parents (informal caregivers) of children with chronic illness or disability (Payakachat et al., 2011).

The HUI is scored by using a multi-attribute utility function to assign weights to each level selected for each attribute (Horsman et al., 2003). The weights are combined statistically to derive a single total utility for the health state. The preference-based scoring functions convert the descriptive health classifications into values for each attribute and a single value for overall

HRQoL. Since the attributes in the HUI are structurally independent, the user can produce attribute scores and overall utility, with scores that range from zero to one, where ‘1’ represents full health and ‘0’ indicates a health state equivalent to dead. Negative values are possible, representing health states worse than dead. The instrument can be an interviewer- or self-administered. The average completion time for the HUI is 5-8 minutes.

4.3.3.3 Parents’ Productivity Losses and Mental Health Service Use

The questionnaire for parents' time losses from and/or usual activities, parents’ change in employment status, and parents' own mental health service utilization due to a child's illness were administered to respondent parents (appendix #). Respondent parents answered parents’ time losses from paid labour and/ usual daytime activities and mental health service utilization questionnaires for both parents. The questionnaire was derived from the Resource Use Questionnaire (RUQ) designed to measure parental and/or caregiver time losses from work and/or usual activities for caregivers of children with chronic illness or disabilities (Tsiplova et al., 2019; Ungar, Tsiplova, Millar, & Smith, 2018).

The mental health questions were designed to capture the mental health services utilization and out-of-pocket costs for parents due to a child’s health and illness. These included a list of mental health service providers, including visits to a family physician, specialists (e.g., psychiatrist, psychologist), primary mental health counsellors or therapists or social workers, other mental health supports programs (such as stress reduction, mindfulness, and yoga) and prescription medications for mental health problems. The respondent parent was asked to indicate whether he/she or his/her spouse/partner used any mental health services for their own mental health because of increased stress or pressure related to caregiving responsibilities and how the service was paid for (e.g., by the Ontario's health care plan, out-of-pocket, by a private insurance program, or in some combination). A twelve-month pre-COVID-19 recall period was used to eliminate the effects of the COVID-19 pandemic on parents' productivity losses and mental health services use. For instance, the respondent was asked: "Over one year, from February 2019 to February 2020, before the COVID-19 pandemic began, on average, approximately how many days did you miss paid employment or your usual daytime activities (routine activities such as household activities, caring for other children, volunteering, attending school, etc.) because you

had to care for your child with ND? Please include personal/sick / vacation leave and any time you took to bring the child to appointments or services related to his/her ND."

4.3.3.4 Care-related Quality of Life Instrument (CarerQol)

The CarerQol measures current well-being (CarerQol-VAS) and subjective burden (CarerQol-7D) of informal caregivers (Appendix I) (Brouwer et al., 2006b). CarerQol-7D and CarerQol-VAS describe the current state of informal caregiving as there is no recall period. Well-being is measured in terms of happiness using a visual analogue scale (VAS) with endpoints 'completely unhappy' (0) and 'completely happy' (10) (CarerQol-VAS). The CarerQol-7D measures subjective burden and is comprised of five negatives (relational problems, mental health problems, problems combining daily activities with care-tasks, financial problems, and physical problems), and two positive (fulfillment from caregiving, social and family support when needed) dimensions of providing informal care. Respondents describe their caregiving situation by selecting one of three possible responses on each dimension: (i) no, (ii) some, and (iii) a lot. Utility tariffs for the CarerQol have been developed to calculate a CarerQol utility score from the responses on the seven dimensions, ranging between 0 ('worst imaginable caregiving situation') and 100 ('best imaginable caregiving situation'). The higher utility scores thus reflect better care-related quality of life. The worst informal care situation is characterized by a lot of problems in all five negative dimensions of providing informal care and no support or fulfilment. The best informal care the best informal care situation is characterized by no problems on any of the five negative dimensions and a lot of support and fulfilment from caregiving. The CarerQol has been used and validated in caregivers of adult and paediatric patients (Biswas et al., 2020; Hoefman et al., 2014; Hoefman, van Exel, Looren de Jong, Redekop, & Brouwer, 2011; Ten Hoopen et al., 2021; Voormolen et al., 2021).

4.3.3.5 Costing

The mean total annual costs per two parents from the parents' payer and societal perspectives were estimated. The parents' payer costs consisted of mental health service providers' costs paid out-of-pocket by parents for their own mental health and parents' productivity costs due to the child's illness. The societal costs consisted of private mental health service providers' costs paid by parents, parents' productivity costs, and publicly funded mental health service provider costs

for parents. With regard to productivity losses, respondent parents were asked to report the average number of missed days from work and/or usual activities for the year before the COVID-19 pandemic. Response options were on an interval scale, e.g., 1 to 5 days, 6 to 10 days, etc. (Appendix # H). If the respondent reported the exact days for missed employment and/or usual daytime activities, the exact day was used to estimate the mean days missed. The average days missed by parents from work and/or usual activities were estimated using the midpoint of the response option. For example, if a respondent parent indicated he/she missed six to ten days of work and/or usual activities, the midpoint ‘eight days’ was used to estimate the productivity losses. The productivity cost was estimated using the human capital approach (Pike & Grosse, 2018; W. B. van den Hout, 2010).The reported days missed from paid employment and/or usual daytime activities were multiplied by the 2021 average Canadian daily wage rate for employees. The average Canadian daily wage rate for employees was estimated by multiplying the 2021 average Canadian hourly wage rate by 7.5 hours (StatisticsCanada, 2022).

A similar approach was applied to estimate the volume (number) of visits to mental health services by respondent parents and their spouses. For instance, if a respondent parent indicated he/she had one to five visits to the psychiatrist for mental health service in a year before COVID-19, the midpoint 'three visits' was used to estimate the total number of visits for that year. The cost of each mental health service was calculated by multiplying the number of visits for that service by the associated fee per visit. Fees for provincially funded professionals such as family physicians, psychiatrists and mental health counsellors were obtained from the Ontario Physician Fee Schedules 2021(Ontario Ministry of Health and Long-Term Care, 2022). Fees for private mental provider services (psychologists and social workers) were obtained from relevant professional associations. Table 4-1 lists sources for all provider fees and rates. Fees for yoga and mindfulness programs were parent-reported.

4.3.4 Analysis

Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to characterize the sample in terms of sociodemographic characteristics and describe the time lost (employment and/or usual daytime activities) and mental health services used by respondent parents and their spouses or partners.

The primary outcomes of interest were HUI (HUI2 and HUI3) score, CarerQol (CarerQol-7D and CarerQol-VAS), mental health care service utilization, and the mean annual costs per two parents from parents' payer perspective due to a child's illness. HUI3 is a recent version of HUI and was developed to address some concerns about the definitions of HUI2 to be applicable in both clinical and general population studies. HUI2 has seven attributes, and HUI3 has eight attributes, as described earlier. Comparing the HUI2 and the HUI3 in the same population can shed light on the influences of different health attributes and scoring functions on utilities in parents of children with ND. For instance, HUI2 assesses self-care directly compared to HUI3, which is relevant for caregivers/parents of children with ND. The mean multi-attribute utility scores for HUI2 and HUI3 for respondent parents and the children were estimated using the respective multi-attribute utility function for HUI2 and HUI3 (Horsman et al., 2003). Furthermore, the mean single-attribute HUI2 and HU3 scores were for respondent parents, and the children were estimated using the respective single-attribute utility function for HUI2 and HUI3. The HUI3 health status classification system describes each subject's (or respondent's) functional ability according to the subject's capacity on eight attributes, and the HUI2 health status classification system describes each subject's functional ability according to the subject's capacity on seven attributes. Single attribute utility functions provide scores that describe the burden of morbidity for a person, attribute by attribute, rather than multi-attribute utility scores of HRQoL for the overall person (Horsman et al., 2003). Each single-attribute utility function (i.e., the set of utility scores for a specific attribute) is defined on a scale from 0.00 to 1.00. The most disabled level of an attribute has a single-attribute utility score of 0.00, and no disability of an attribute has a single-attribute utility score of 1.00 (Horsman et al., 2003; Torrance, Furlong, & Feeny, 2002).

Tariffs for CarerQol-7D are available, and the total CarerQol utility scores for CarerQol states can be calculated by adding up the tariff per category of the seven CarerQol-7D dimensions, which represents informal care situation in utilities ranging from 0 (worst informal caregiving situation) to 100 (best informal caregiving situation) (Brouwer et al., 2006b). CarerQol-7D tariffs for Australia, Germany, Sweden, UK, US, and the Netherlands (Hoefman, van Exel, & Brouwer, 2017). Tariffs for the CarerQol-7D were based on preferences of the general public of the respective country for different care situations as described with the seven dimensions (and three

levels) of the instrument. To date, no tariff sets for the CarerQol-7D exist for Canada (Hoefman et al., 2017). The CarerQol utility score was estimated using US traffic (Hoefman et al., 2017).

The mean annual costs for respondent parents were estimated by summing up the average annual productivity and mental health provider service costs. The mean total annual cost per two parents was from a parents' payer perspective was estimated by adding the mean annual cost for respondent parents and their spouses or partners. The parents' payer costs consisted of mental health service providers' costs paid out-of-pocket by parents for their own mental health and parents' productivity costs due to the child's illness. In addition, the mean total annual costs per two parents from a societal perspective was estimated. The societal costs consisted of private mental health service providers' costs paid by parents, parents' productivity costs, and publicly funded mental health service provider costs for parents.

4.4 Results

4.4.1 Sample Characteristics

A total of 53 parents and their children provided consent and assent. Six children (and their parents) were excluded from analyses because they did not have ND. Therefore, 47 parents and their children with ND (patients) participated in the research. Table 4-2 presents the demographic characteristics of respondent parents and patients with ND. The mean age of children with ND was 12.02 years (SD: 3.34; ranging from 6 to 18 years). Fifty-one percent of children were male, and 49% were female. Of 47 patients, 13 patients were diagnosed with Mono-ADS, ten patients were diagnosed with AE, seven were diagnosed with MS, five were diagnosed with MOG-IgG related recurrent disease, five had CNS inflammatory disease but diagnosis not known, four were diagnosed with systematic and CNS inflammation and three with NMOSD.

The mean age of respondent parents was 43.76 years (SD: 6.31; range from 29 to 57 years). The majority of respondent parents were female (79%), married (96%), working full-time or part-time (79%) and had an associate (or some college credit) or bachelor's or master's degree (96%). Fifty-three percent of respondent parents indicated they were equally responsible as their spouses or partners for the care and upbringing of the child (equal caregivers), and 45% reported being primary caregivers. Fifty-five percent of respondent parents reported that their yearly household

income was over $100k, and 21% reported their annual household income was between $75k to $99,999. A higher proportion of respondent parents were White (51%), followed by South Asian (17%) and others (32%).

4.4.2 Health-Related Quality of Life of Respondent Parents and their Children

Table 4-3 shows the mean HUI2 and HUI3 multi-attribute scores by disease categories and overall sample for both patients and respondent parents. The severity of symptoms can vary across the NDs. For example, MS, if not well controlled, is characterized by relapses which lead to worsening of neurological status and recovery, while other neuroinflammatory disorders might result in irreversible motor disability after one event, e.g., acute flaccid myelitis, which frequently leads to irreversible paralysis (O'Mahony et al., 2019). The original intent of this study was to conduct a comparative analysis of HUI2 and HUI3 scores among several types of ND. However, we could not compare utility scores across the type of NDs because of lack of adequate sample sizes. The mean [SD] multi-attribute utility score or the overall sample of patients using HUI3 was (0.81 [0.24]) and using HUI2 was (0.84 [0.17]).

As seen in Table 4-4, respondent parents' mean single-attribute utility scores on sensation, emotion, and pain in HUI2 were lower than 1.00. Similarly, respondent parents' scores in single-attribute utility on emotion and cognition in HUI3 were lower than 1.00. These single-attribute utility scores suggest some functional impairments on respective attributes (Horsman et al., 2003). However, it is difficult to conclude that these functional impairments are family health spillovers due to children's ND on respondent parents without a control group of parents of healthy children and/or analyzing single-attribute utility scores using longitudinal data.

Guertin and colleagues estimated the age and province-specific utility scores norms based on the 2013-2014 Canadian Community Health Survey (CCHS) (Guertin, Feeny, & Tarride, 2018). Table 4-5 shows the mean HUI3 multi-attribute utility scores of respondent parents and the mean- HUI3 multi-attribute scores of the Ontario general population by age groups.

4.4.3 Care-related Quality of Life of Parents

Table 4-6 presents the results from CarerQol (CarerQol-7D and CarerQol-VAS) instrument. Out of 47, 44 (94%) respondent parents of children with ND derived some or a lot of fulfillments from caring for their child. Nearly all respondent parents reported (87%) that they had no relationship problems with the care receiver, the child. More than half of the respondent parents had some or a lot of mental health problems, which confirmed to some extent the findings from single attribute scores in HUI2 and HUI3. As seen in Table 4, the estimated mean single-attribute utility scores for emotion attributes were lower than '1.00', suggesting some functional impairments in emotion. Approximately 38% of respondent parents experienced problems combining their care tasks with daily activities The majority of respondent parents (77%) had some or a lot of support from family and friends when needed. The mean total CarerQol utility score was 85.97 (SD: 11.94), ranging from 57.8 to 100.1. Finally, on average, respondent parents scored a 7.68 (SD: 1.08) on the CarerQol-VAS.

4.4.4 Parental Time Losses from Work and/or Usual Activities

Table 4-7 presents the days lost from paid labour and/or usual daytime activities missed by the respondent parents and their spouses or partners due to a child's health or illness. Out of 36 respondents, 31 (86%) respondent parents reported they had missed their days from paid labour and/or usual daytime activities for the year prior to COVID-19 because they had to care for a child with ND. Respondent parents' mean annual days lost from paid labour and/or usual daytime activities was 19.86 days (median:8, ranging from 0 to 240). The number of days missed by respondent parents varied from 1 to 5 days to 60 days or more. Furthermore, out of 36, 13 (36%) respondent parents reported their paid employment status was affected by having a child with ND during the year prior to COVID-19. Among 13 respondent parents whose employment status was affected, 11% (n=4) took unpaid leave, 8 % (n=3) had reduced hours at work, 5% (n=2) quit job, 5% (n=2) changed part-time to a full-time a job, and 5% (n=2) used sick days or vacation time to provide the care for the child.

Over 78% of respondent parents reported that their spouses or partners had missed paid labour and/or usual daytime activities a year prior to COVID-19 because they had to care for a child with ND. The mean annual days missed from paid labour and/or usual daytime activities by

respondent parents' spouses or partners was 11.68 days (median: 3, ranging from 0 to 180). Similar to respondent parents, the number of days missed by their spouses or partners varied from 1 to 5 days to 60 days or more. Furthermore, out of 36, 8 (22%) respondent parents reported that their spouses' or partners' employment status was affected by having a child with ND during the year prior to COVID-19. Among eight respondent parents' spouses or partners, 8% (n=3) had reduced hours at work, 5% (n=2) quit a job, 5% (n=2), and 2.77% (n=1) changed a full time to part job to provide care for the child.

4.4.5 Mental Health Care Utilization by Parents

As shown in Table 4-8, 22% (8 out of 36) respondent parents used one or more mental health services during the year prior to COVID-19 for mental health concerns caused by stress or pressure related to caregiving responsibilities for children with ND. Respondent parents received services from various mental health service providers. The visits to the family physician (8 %) and yoga and mindfulness programs (8%) were the most common types of mental health services received by respondent parents.

Relatively few numbers of spouses or partners of respondent parents (3 out 41; 8%) used mental health services in the year prior to COVID-19 for mental health concerns caused by stress or pressure related to caregiving responsibilities for children with ND compared to respondent parents, with visits to the family physician (5%) most common.

4.4.6 Parents Costs and Societal Costs

Table 4- 9 shows the mean annual costs associated with types of mental health services and mean total annual costs per two parents from the parents' payer and societal perspectives. The distribution of mental health care costs for parents was right-skewed, with a small proportion of respondent parents and their spouses or partners reporting very high costs. The mean annual cost for mental health services for two parents was CAD 262, with a median of zero ranging from CAD 0 to CAD 2,803. The costs per two parents from the parents' payer perspective and societal costs were characterized by skewness and high variance due to some participants having high costs. The mean annual cost per two parents from the parents' payer perspective was CAD 7,366, with a median of CAD 2,477 ranging from CAD 0 to CAD 63,077. The mean annual

productivity cost for two parents was CAD 7104 with a median of CAD 2,476, ranging from CAD 0 to CAD 60,810 and was the most significant contributor to parents' total costs. Finally, the average total annual societal cost per two parents due to the child's health illness was CAD 7,401, with a median of CAD 2,477 ranging from CAD 0 to CAD 63,584.

4.5 Discussion

This study aimed to assess HRQoL and care-related quality of life of parents of children with ND. This study also sought to measure the mental health resource utilization and the associated mental health resource use costs and productivity costs associated with parental time losses from work or usual activities for parents of children with ND. The results from this study indicated reduced HRQoL (based on scale '0' dead and '1' perfect health), care-related quality of life and time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND. Consequently, there are associated costs for the parents and/or caregivers. The lack of a control group of parents of healthy children limits the ability of this study to infer respondent parents' HRQoL as *family health spillover effects* and mental health resource use cost and productivity cost of respondent parents and their partners or spouses as *family cost spillover effects* on parents of children with ND. Moreover, because of our inability to establish the causal relationship between a child's ND and family spillover effects, we could not conclude whether the empirical evidence from this cross-sectional empiric study supports our hypothesized interrelationship between synthesized constructs and concepts in the proposed theoretical framework in Chapter 3. Nevertheless, it supports our rationale why it is challenging to measure the family health spillover effects using an isolated approach-as isolated quantity and an inherent method' is preferable in the context of pediatric CUAs (Section 3.3.5.1.2, Chapter 3).

Published reports on family cost and heath spillover effects on parents and/or caregivers of children have been limited. The results from this study provide a starting point for measuring family and health and cost spillover effects in the context of pediatric CUA and opening the door for comparative analyses. Future studies should measure family health and cost spillover effects of parents and/or caregivers of children with ND using a comparison group of parents and/or caregivers of healthy children and longitudinal data with larger sample sizes. Furthermore, the

findings can be used in incorporating family health and cost spillover effects in model-based economic evaluation of interventions or treatments for children with ND.

The estimated mean multi-attribute utility scores (HUI2 and HUI3) capture the HRQoL of respondent parents of children with ND. These health scores may include the impact of having a child with ND (if there is any) and the underlying health of respondent parents. For instance, caregiving may have a negative effect on respondent parent HRQoL (utility score), but existing health conditions in respondent parents may also affect their HRQoL. The independent disutility (or utility increments) associated with *caring for* and *caring about* a child with ND should be assessed to estimate family health spillover effects on respondent parents (Chapters 1 and 3). A recent systematic review of studies measuring quality of life using different HRQoL instruments found that parents of children with rare diseases, including ND, experienced reduced overall quality of life compared to parents with healthy children and compared to norm values (Boettcher, Boettcher, Wiegand-Grefe, & Zapf, 2021). Further research with control parents of healthy children is required to make valid conclusions regarding the impacts of children with ND on parents' HRQoL.

With regard to single attribute scores, respondent parents' scores in single-attribute utility on emotion and pain in HUI2 and HUI3 were lower than 1.00 (on scale 0 to 1, 0= lack of functional capacity 1=full function), indicating some functional impairments in emotional and physical (pain) well-being. Again, it is difficult to establish causal relationships between children's ND and respondent parents' emotional and physical well-being without a control group of parents of healthy children. These functional impairments could be due to their respondent parents' own health and/or effects of COVID-19. The data collection of this study was conducted during the COVID-19 pandemic. Studies have shown the psychological impact of the COVID-19 pandemic on the general population (Amerio et al., 2020; Serafini et al., 2020). Another factor that might have impacted respondent HRQoL in this study is the time of diagnosis. The diagnosis of disease (s)for most patients (76%, 36 out of 47) in this study happened before February 2020. The time between the interview and diagnosis is at least eight months. For some respondent parents, the time is more than a year. Parents may have become resigned to the fact that their child has a ND and adapted to caring for a child with ND. Therefore, lesser impacts on respondent parents' HRQoL at the time of the interview. Studies have shown that parents and/or caregivers of

children with chronic illness or disabilities experienced higher parental stress and anxiety at the initial time of diagnosis compared to years after diagnosis (Boman, Lindahl, & Björk, 2003; Stuart & McGrew, 2009). Having said that, it is important to discuss findings from previous findings regarding parents' and/caregivers' mental and physical health.

In a comparative study of 156 mothers of children with MS and 624 mothers of children without MS, the mothers of children with MS reported a higher prevalence of physical pain and mood and anxiety disorders compared to mothers of children with MS (Marrie et al., 2020). In a separate prospective study, the HRQoL of parents of children with two types of ND was assessed using the Pediatric Quality of Life Inventory (PedsQL™) Family Impact Module (O'Mahony et al., 2019). Parents of children with MS reported greater emotional dysfunction and worry compared to parents of children with monoADS. Caregiving for adults with MS has also negatively affected caregivers' emotional and physical well-being (R. J. Buchanan, Radin, & Huang, 2011). Moreover, a recent systematic review of the needs and experiences of children and adolescents with pediatric MS and their caregivers concluded that caregivers experienced negative impacts on social functioning, mental health, and quality of life (Ghai et al., 2021). Other chronic childhood illnesses or disabilities, including cerebral palsy, autism spectrum disorder, epilepsy, and attention deficit disorder, have been correlated with parents' high emotional and physical distress (Boettcher et al., 2021; Savage & Bailey, 2004).

Parents' worries about their children's future, disruptions in parents' professional careers and personal relationships, and parents' guilty feelings or self-blame may explain the poor emotional HRQoL (Chapter 1). Studies have shown that parents of children with chronic illness or disabilities frequently worry about their future and their children's future (Christina A Martin, Nicole Papadopoulos, Tayla Chellew, Nicole J Rinehart, & Emma Sciberras, 2019; Zebrack et al., 2002). This prolonged worry may adversely affect the mental well-being of parents. Some parents may feel guilty or experience self-blame for not being able to provide what they perceive as a sufficient amount of care for a child despite their full commitment to them and not spending a sufficient amount of time with their other healthy children, if applicable (Findler et al., 2016; Golla et al., 2015). In addition, providing informal care for prolonged periods can induce detrimental effects on the parents' and/or caregivers' physical health. These effects are primarily related to caregiving activities — for example, physical strain from lifting and dressing a child or

fatigue from hours of informal caregiving. A few studies examining the physical health of parents of children with disabilities reported poorer physical health outcomes than the parent of typically developing children (M. H. Lee et al., 2017; Lovell et al., 2012).

Regarding the care-related quality of life, the respondent parents reported being relatively happy, scoring more than a seven on a 0-10 scale of happiness. Published reports on the use of the CarerQol instrument to measure the care-related quality of life in caregivers and/or parents of children or adults with ND are limited. The finding from the present study was consistent with previous findings from studies that have used CarerQol to measure the care-related quality of life of caregivers and/or parents of children with other chronic illnesses or disabilities, such as autism spectrum disorder (ASD), epilepsy, and cystic fibrosis (Fitzgerald, George, Somerville, Linnane, & Fitzpatrick, 2018; Hoefman et al., 2014). Hoefman et al., used the CareQol instrument to measure the carer-related quality of life of parents and/or caregivers of children (mean age 8.4 years) with ASD. The mean [SD] CarerQol-VAS score was 7.4 (1.9). Similar to our finding (94%), all most all caregivers (97%) derived a lot or some fulfillment from caring for their child with ASD. Furthermore, more than half of the respondent parents in our study experienced some or a lot of problems with their own mental health due to caregiving responsibilities, which is consistent with the findings from Hoefman et al.'s study on caregivers of children with ASD and Fitzgerald et al., study on caregivers of children with cystic fibrosis (Fitzgerald et al., 2018; Hoefman et al., 2014). In both studies, more than half of the caregivers and/or parents reported mental health problems due to caregiving responsibilities. The mean (SD) total CarerQol utility score for respondent parents and/or caregivers in this study was 85.97 (11.94), ranging from 57.8 to 100.1. In a Canadian study of caregivers of children (aged 4 to 18 years) with epilepsy, the authors' estimated mean total CarerQol utility score was 81.35 (SD:17.04; range 22.80–100.10) (Jain, Subendran, Smith, & Widjaja, 2018). This study also used the US traffic to derive the utility score for caregivers and/or parents.

One of the advantages of using the CarerQol instrument to measure the family spillover effect is that this instrument was developed to measure caregiver burden and care-related quality of life and, therefore, the estimated utility score from this instrument reflects the overall impact of the caregivers (Brouwer et al., 2006b). Other generic preference HRQoL instruments, such as HUI-2 and HUI-3 used in this study, were designed to measure the HRQoL of general population.

These generic measures may not disentangle the effects of caregiving from other aspects of life that may affect caregivers/parents' HRQoL, such as their own health conditions. However, as discussed in chapters 1 and 2, family health spillover effects stem from family effects, 'caring about other' and caregiving effects, 'caring for other.' Since the CarerQol instrument was specifically developed to measure caregiving effects, this instrument may not measure family effects, 'caring about others.'

This study results showed that approximately 22% of respondent parents and 8% of their spouses or partners visited mental health service providers for mental health concerns caused by stress or pressure related to caregiving over a one-year period. The authors are unaware of other studies that have examined the rate of overall mental health services used by parents and/caregivers of children with ND of their own mental health problems caused by stress related to caregiving. Recently, Marrie et al. compared the rates of different types of mental health services (hospitalization, primary care physicians visits, and psychiatry visits) and in mothers of children with MS with mothers without MS using population-based administrative data from Ontario, Canada (Marrie et al., 2020). In comparison with 624 mothers of children without MS, the 156 mothers of children with MS did not a higher rate of physician visits compared to non-MS-mothers. In contrast, mothers with MS had increased odds of having any psychiatry visits (OR 1.60; 95% of CI 1.10–2.31). In this study, the most common mental health service used by respondent parents were family physician visits (8.33%, three out of 36), and psychiatrist (8.33%, three out of 36). Similarly, the most common mental health service used by respondent parents' spouses or partners were family physician visits (5.56%, two out of 36). It is difficult to make any conclusion regarding the causal relationship between a child's ND and parents' mental health services use without a control group of parents of healthy children.

The majority of respondent parents and their spouses or partners missed work and/or usual daytime activities to provide care for the affected child. Researchers are unaware of any studies that have reported mean annual days missed by parents to compare. In this study, 36.11 % respondent parents and/or caregivers reported their paid employment status was affected by having a child with ND 11.11 % took unpaid leave, and 8.33% had reduced hours at work. One Canadian study estimated mothers of children with disabilities are 3 to 11% less likely to work, and the effect (13 to 15%) is larger if the child is severely disabled (Stabile & Allin, 2012).

Tsiplova et al., measured the resource utilization and cost for pre-school children with ND in two Canadian Provinces Nova Scotia (NS) and New Brunswick (NB) (Tsiplova et al., 2019). In that study, 50 to 57% of respondent parents in NB reported that their employment status was affected by having a child with ASD at baseline or 12 months' follow-up. Furthermore, eight percent said they had to reduce working hours to care for children with ASD (Tsiplova et al., 2019).

The mean productivity costs incurred by two parents in the year before COVID-19 was estimated at CAD 7104, ranging from CAD 0 to CAD 60,810. Published studies on productivity losses by parents and/caregivers of children with ND have been limited. One Canadian study estimated the cost of caregiver time lost per patient according to the Expanded Disability Status Scale (EDSS) score of adults with MS. The EDSS is a method of quantifying disability in MS (Grima et al., 2000). The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability (Kurtzke, 1983). The authors estimated average annual productivity cost for caregivers of children with MS in 1997 ranges for CAD 3,123 for low disability (EDSS 1) to CAD 5,914 for high disability (EDSS 6).

Increased time commitment is required for caregiving when a child is diagnosed with ND when compared with a healthy child. This reduces the time available to parents and/or caregivers for other activities, including work, leisure activities, and personal care. Even when the parents are working, time restrictions mean that they frequently must rely on sick, vacation or un-paid leaves to take the child to medical appointments or other services. Relatively few studies have estimated the cost of time loss (workdays and usual activities) for parents and/or caregivers of children with ND compared to parents and/or caregivers of other disabilities or illnesses (A. M. Kish, P. A. Newcombe, & D. M. Haslam, 2018; Naci et al., 2010; Shahat & Greco, 2021). For instance, Tsiplova et al. estimated productivity costs (productivity losses from paid employment and usual daytime activities) for parents of children with ASD ranging from CAD 2719 to 9062 CAD per child per year.

It is essential to include financial impacts on parents while estimating the total burden of ND. More importantly, a decrease in time availability for work, leisure activities and self-care activities may affect the sense of control a parent has over their life and hence, impacts mental and psychological well-being (Brandon, 2007; Janneke Hatzmann et al., 2014). Future studies

should measure the time lost by parents and/or caregivers of children with ND using a comparison group of parents and/or caregivers of healthy children and longitudinal data with larger sample sizes.

The estimated average total annual cost per two parents from the parents' payer perspective was CAD 7366. The productivity cost (paid labour and/or usual daytime activities) of caregivers and/or parents was substantial. This speaks to the emotional and psychological burden of ND on parents and caregivers. From a societal perspective, the estimated mean total annual cost per two-parent was CAD 7401. Studies that report the total cost of mental health service utilization and productivity losses from paid labour for parents of children with ND due to a child's illness are rare. This study attempted to measure the cost spillover effects for parents of children with ND. It is important to note that the distribution of costs for most categories were right skewed with a small proportion of respondent parents reporting very high costs. For instance, one respondent parent reported that he/she missed 240 days from paid labour and/or usual activities to provide care for a child with ND and had very high productivity costs compared to other respondent parents. A small proportions of respondent parents and their spouse or partners used the mental health services for mental health problems caused by stress or pressure related to caregiving responsibilities.

Overall, the results indicated reduced HRQoL (based on scale '0' dead and '1' perfect health), carer-related quality of life, time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND Consequently, there are associated costs for the parents and society. However, because of a lack of a control group of parents of healthy children and/or longitudinal data, it was difficult to conclude that these impacts are family health and cost spillover effects on parents and/or caregivers. The family health and costs spillover effects are often ignored in estimating the total burden of pediatric ND and/or effectiveness of interventions or treatments for children with ND. It is essential to measure and include the parental cost in the cost of illness studies to estimate the full economic burden of pediatric ND. Also, it is important to measure and include family health and cost spillover effects on parents (and other family members) in economic evaluation of alternative treatments or interventions for children with ND.

Furthermore, understanding the impacts of pediatric ND on the physical, mental, social, and economic well-being of parents and caregivers is essential to know the needs of parents and caregivers. The needs of parents and caregivers are often overlooked in efforts to provide the best care for the patient. The information on the impacts on parents and caregivers may encourage healthcare providers, including pediatricians, pediatric neurologists, family physicians, and others involved in the child's care, to coordinate with mental health services providers, such as psychologists, social workers, and mental health counsellors, for psychological support to parents and caregivers. Research has shown that mental health interventions for parents and/or caregivers of chronically ill patients reduce anxiety and depression and improve the overall quality of life of parents and/or caregivers (Cherak et al., 2021; Wiegelmann, Speller, Verhaert, Schirra-Weirich, & Wolf-Ostermann, 2021). The finding from this study that having a child with ND may impacts the labour time of parents and/or caregivers could be informative for policymakers. Providing financial support or access to mental health interventions alleviates the mental stress of families. Policies should target parents and caregivers from marginalized and vulnerable groups such as new immigrants, indigenous communities, rural and remote communities that endure the significant effects.

4.6 Limitations

This study had several primary limitations. Firstly, the study design was cross-sectional and lacked a control group of parents of healthy children. Therefore, it was difficult to establish a causal relationship between pediatric ND and respondent parents' HRQoL and CarerQol. Furthermore, it limited the possibility of determining the causal effect between pediatric ND and productivity losses and mental health service utilization of parents. Secondly, the sample size of this study was only 47 (36 for costs data), which reduced the statistical power and the ability to test HUI2 and HUI3 across the types of ND. Many factors such as parents' own health and family members' health influence the parents' HRQoL and employment and/or usual daytime activities. This study was unable to evaluate the effects of these factors. The recall bias may be an issue in this study. To eliminate the effect of the COVID-19 pandemic, the research (RL) asked respondent parents to remember the number of days missed paid labour and/or usual daytime activities and the average number of visits to mental health services a year before the COVID-19 pandemic (February 2019 to February 2020). The data collection of this study ended

in January 2022. Some respondent parents and/or caregivers had to go back two years to remember their time losses in paid labour and/or usual daytime activities spouses or partners' mental health service uses. Finally, fifty-five percent of respondent parents reported that their yearly household income was over $100k. The median after-tax income of Canadian families and unattached individuals was $66,800 in 2020 (StatisticsCanada, 2022). Therefore, this sample may not represent the general population, and the findings cannot be generalized to the population as a whole.

4.7 Conclusion

The results from this cross-sectional study indicated reduced HRQoL (based on scale '0' dead and '1' perfect health) , carer-related quality of life, time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND. These data are limited by their cross-sectional data. Our lack of longitudinal data and a control population limits the ability to draw definitive conclusions regarding spillover effects in this population. Further research with a comparison group of parents and/or caregivers of healthy children and a larger sample is required to determine the family health and cost spillover effects in parents of children with ND.

Table 4-1 Private and Public Mental Health Service Provider Rates

Service	Payer	Price (per visit)	Billing Code	Year	Source
Family physician (consultation or general assessment per visit)	Public	84.45	A003	2021	(Ontario Ministry of Health and Long-Term Care, 2022)
Psychiatrist (consultation per visit)	Public	215.65	A195	2021	(Ontario Ministry of Health and Long-Term Care, 2022)
Mental health counsellor* (consultation per visit of primary mental health care)	Public	67.75	K005	2021	(Ontario Ministry of Health and Long-Term Care, 2022)
Social worker (hourly consultation fee)	Family	130		2021**	(Canadian Assoication of Social Workers, na)
Psychologist (hourly consultation fee)	Family	225		2021**	(Ontario Psychological Association, na)
Yoga and mindfulness programs (per single session)	Family	25		2021	Respondent parents reported

OHIP, Ontario Health Insurance Plan

All prices re reported in 2021 Canadian dollars.

* The respondent parents reported that they had received mental health services from mental health counsellors, and the cost was covered by Ontario Health Insurance Plan (OHIP). But respondent parents did not provide any further detail. To estimate the cost, the researcher (RL) assumed that respondent parents had received the mental health service from the primary mental care provider.

** Fees for social workers and psychologists are recommended by the Canadian Association of Social Workers and Ontario Psychological Association, respectively. Fees per hour listed in the table are recent and assumed to be recommended for 2021.

Table 4-2 Patient and Parent Demographics (n=47)

	n	Percentage (%)
Child		
Age		
Mean, years (SD)	12.02 (3.34)	
Range	6 to 18	
Sex		
Male	24	51.06
Female	23	48.94
Parent		
Age		
Mean age, years (SD)	43.76 (6.31)	
Range	29 to 57	
Respondent's gender		
Female	37	78.72
Male	10	21.28
Relationship of respondent to the child		
Mother	36	76.60
Father	10	21.28
Stepmother	1	2.13
Role of respondent in the child's care		
Primary Caregiver	21	44.68
Equal Caregiver	25	53.19
Secondary Caregiver	1	2.13
Marital status of respondent		
Married or living common-law	45	95.74
Separated or divorced	2	4.26
Education of respondent		
Grade 12 or less	1	2.13
Completed high school	1	2.13
Associate degree or some college credit	14	29.79
Bachelor's degree	23	48.94
Master's degree	8	17.02
Respondent's population group		
White	24	51.06
South Asian	8	17.02
Others	15	31.91
Employment status of respondent		

Working full-time	29	61.70
Working part-time	8	17.02
Temporarily laid off/ looking for work or unemployed	3	6.38
Staying at home or caregiver	7	14.89
Total household income		
Less than $34,999	2	4.26
$35,000 to $49,999	2	4.26
$50,000 to $74,999	6	12.77
$75, 000 to $99,999	10	21.28
$100,000 to $199,999	20	42.55
$200,000 and over	6	12.77
Missing % (n)	1	2.13

* Age at the time of the interview. The respondent was asked about the child's date of month and year, and his or her age in years.

Table 4-3 HUI2 and HUI3 Multi-attribute Utility Scores of Respondent Parents and their Children by Type of ND (n=47)

Type of ND		**HUI-2, mean (SD)**				**HUI-3, mean (SD)**		
	Children*	n	Respondent parents**	n	Children*	n	Respondent parents**	n
Mono-ADS	0.83 (0.19)	10	0.86 (0.17)	13	0.85 (0.19)	11	0.82 (0.27)	13
NMOSD	0.70 (0.23)	3	0.88 (0.09)	3	0.78 (0.17)	3	0.70 (0.24)	3
MOG-IgG related disease	0.89 (0.07)	5	0.90 (0.08)	5	0.94 (0.05)	5	0.94 (0.03)	5
MS	0.89 (0.11)	6	0.95 (0.05)	6	0.83 (0.17)	7	0.92 (0.08)	7
AE	0.80 (0.25)	10	0.95(0.04)	10	0.71 (0.39)	10	0.93 (0.09)	10
Systematic & CNS inflammation	0.94 (0.02)	3	0.82 (0.11)	3	0.93 (0.06)	3	0.82 (0.19)	3
CNS inflammatory but diagnosis is not known	0.83 (0.11)	5	0.97 (0.04)	5	0.69 (0.28)	5	0.97 (0.03)	5
Overall sample	*0.84 (0.17)*	*42*	*0.91 (0.11)*	*45*	*0.81 (0.24)*	*44*	*0.88 (0.18)*	*46*

Mono-ADS monophasic acquired demyelinating syndrome, *NMOSD* neuromyelitis Optica spectrum disorder, *MOG-IgG* myelin oligodendrocyte glycoprotein, *MS* multiple sclerosis, *AE* autoimmune encephalitis, *CNS* central nervous system

*An interview-administered parent-proxy assessed HUI was used for children with ND

**An interview-administered self-assessed HUI was used for respondent parents

Table 4-4 HUI2 and HUI3 Single Attribute and Multi-Attribute Utility Scores (n=47)

	Children with ND*	**Respondent parents****
HUI2 single attributes scores	Mean utility (SD)	Mean utility (SD)
Sensation	0.95 (0.15)	0.94 (0.06)
Mobility	0.94 (0.16)	0.99 (0.01)
Emotion	0.83 (0.23)	0.93 (0.11)
Cognition	0.94 (0.07)	0.97 (0.06)
Self-care	0.91 (0.28)	1.00 (0.00)
Pain	0.95 (0.09)	0.95 (0.11)
HUI3 single attributes scores		
Vision	0.99 (0.01)	0.97 (0.02)
Hearing	0.99 (0.04)	0.99 (0.02)
Speech	0.95 (0.20)	1.00 (0.00)
Ambulation	0.94 (0.21)	1.00 (0.00)
Dexterity	0.96 (0.16)	1.00 (0.00)
Emotion	0.91 (0.12)	0.94 (0.11)
Cognition	0.92 (0.14)	0.96 (0.11)
Pain	0.92 (0.15)	0.93 (0.18)

*An interview-administered parent-proxy assessed HUI was used for children with ND
**An interview-administered self-assessed HUI was used for respondent parents

Table 4-5 Comparison of the Mean HUI3 Multi-Attribute Utility Scores of Respondent Parents and Ontario General Population Norms by Age Groups

Age Range (years)*	Sample HUI3 utility scores **			Ontario HUI3 utility scores***		
	Mean	Median	Interquartile range	Mean	Median	Interquartile range
35 to 39, (n=8)	0.82	0.93	0.11	0.88	0.94	0.12
40 to 44, (n=15)	0.92	0.93	0.09	0.88	0.94	0.11
45 to 49, (n=11)	0.84	0.97	0.14	0.86	0.92	0.12
50 to 54, (n=8)	0.93	0.95	0.07	0.83	0.92	0.13

*Respondent parents' age in this study ranged from 29 to 57 years. However, the age group 29 to 34 and 55 to 57 were not compared because of the small sizes.

** An interview-administered self-assessed HUI was used for respondent parents

*** These data were derived from Guertin et al., 2018

Table 4-6 Respondent Parents' Care-related Quality of Life (n=47)

	n	Percentage (%)
CarerQol-7D		
Domains		
Fulfillment		
No	3	6.38
Some	17	36.17
A lot of	27	57.45
Relationship problems		
No	41	87.23
Some	6	12.77
A lot of	0	0.00
Mental health problems		
No	24	51.06
Some	20	42.55
A lot of	3	6.38
Problems combining daily activities		
No	29	61.70
Some	17	36.17
A lot of	1	2.13
Financial problems		
No	29	61.70
Some	15	31.91
A lot of	3	6.38
Support from family and friends		
No	11	23.40
Some	22	46.81
A lot of	14	29.79
Physical health problems		
No	34	72.34
Some	13	27.66
A lot of	0	0.00
Total utility score for caregiver QOL, mean (SD)	85.97 (11.94)	
CarerQol-VAS (0-10), mean (SD)	7.68 (1.08)	

Table 4-7 Days Lost from Paid Labour and/or Usual Daytime Activities by Parents due to a Child with ND Health or Illness from February 2019 to February 2020 (n=36)

	n	**Percentage (%)**
Respondent parent	36	
Days lost from paid labour and/or usual daytime		
Yes	31	86.11
No	5	13.89
Days lost from paid labour and/or usual daytime, mean (SD)	19.86 (41.93)	
Respondent's spouse or partner	36	
Days lost from paid labour and/or usual daytime		
Yes	28	77.78
No	8	22.22
Days lost from paid labour and/or usual daytime, mean (SD)	11.68 (30.58)	

***** Eleven respondents were not applicable because their child's disease diagnosis occurred after February 29, 2020, and they were therefore excluded while estimating days lost from paid labour and/or usual daytime activities by the respondent parent and his or her spouse or partner

Table 4-8 Mental Health Services Used by Respondent Parents and their Spouses or Partners due to a Child with ND Health or Illness from February 2019 to February 2020 (n=36)

Service	n	Percentage (%)
Respondent parent		
Any mental health service used due to a child's illness or disability		
Yes	8	22.22
No	28	77.78
*Types of mental health service**		
Family physician		
Yes	3	8.33
No	33	91.67
Psychiatrist		
Yes	3	8.33
No	33	91.67
Social worker or psychologist		
Yes	2	5.56
No	34	94.44
Other service(s) for mental health (yoga and mindfulness programs)		
Yes	2	5.56
No	34	94.44
Respondent's spouse or partner		
Any mental health service used due to a child's illness or disability		
Yes	3	8.33
No	33	91.67
*Types of mental health services**		
Family physician		
Yes	2	5.56
No	34	94.44
Mental health counsellor or psychiatrist		
Yes	2	5.56
No	34	94.44

* Not mutually exclusive. Parent(s) may have used more than one type of mental health service
**Eleven respondents were not applicable because their child's disease diagnosis occurred after February 29, 2020, and they were therefore excluded while estimating mental health service use by the respondent parent and his or her spouse or partner

Table 4-9 Total Annual Average Cost of Mental Health Services and Productivity Losses Cost for Two Parents (Respondent and Spouse or Partner) from February 2019 to February 2020 (n=36)

Service	Mean	Median	Range
Types of mental health services			
Family physician	35	0	0 to 506
Psychiatrist	162	0	0 to 2803
Mental health counsellor	15		0 to 542
Social worker or psychologist	66	0	0 to 2365
Other service(s) for mental health (yoga and mindfulness programs)	19	0	0 to 375
Total mental health services use costs*	262	0	0 to 2803
Productivity costs			
Cost of parents' time losses from paid labour and/or usual daytime activities	7104	2476	0 to 60810
Total costs per two parents from the parents' payer perspective**	7366	2477	0 to 63077
Total costs per two parents from a societal perspective***	7401	2477	0 to 63584

All costs in 2021 Canadian dollars

* Total mental health services use costs are respondent parent's and spouse's or partner's private mental health service uses costs to cope with increased stress or pressure related to caregiving responsibilities

** Total costs per two parents from the parents' payer perspective consists of costs of respondent parent's and spouse's or partner's private mental health service uses and times losses from work and/or usual activities due to caregiving responsibilities for children with ND

*** Total costs per two parents from a societal perspective include respondent parent's and spouse's or partner's private mental health service uses, public mental health service uses, and times losses from work and/or usual activities

5 Discussion

This chapter summarizes and integrates the key findings of this thesis, discusses their implications for various stakeholders, recommends future research, and ends with concluding remarks. The primary aim of this thesis was to develop a theoretical framework for incorporating family health and cost spillover effects in pediatric economic evaluation. A further aim was to propose an approach for including family health and cost spillover effects in pediatric cost-utility analysis (CUA) based on the theoretical framework. These aims were met with three research endeavours:

1. A systematic review was conducted to summarize the methods used in pediatric CUAs to include family health spillover effects and maternal-perinatal CUAs to integrate the health outcomes of pregnant women and children (see Chapter 2)
2. A critical interpretative synthesis of the existing theories, conceptual frameworks, and models was carried out to develop a theoretical framework to incorporate family spillover effects in pediatric economic evaluation (see Chapter 3)
3. A cross-sectional study was conducted to measure the health-related quality of life (HRQoL), care-related quality of life, mental health service use and time losses from paid labour and/or usual activities of parents and/or caregivers of children with a neuroinflammatory disorder (ND) (s) (see Chapter 4)

The systematic review of the literature (Chapter 2) informed the critical interpretative synthesis (Chapter 3), and the theoretical framework developed in critical synthesis informed the data collection, analysis, and interpretation of HRQoL, care-related quality of life, mental health service use and time losses from paid labour and/or usual activities of parents and/or caregivers of children with ND (Chapter 4). A brief summary of each chapter is presented in the following sections.

5.1 Summary of Main Findings

5.1.1 Systematic Review of Methods Used by Pediatric CUAs to Include Family Health Spillover Effects and Maternal-perinatal CUAs to Integrate the Health Outcomes of Pregnant Women and Children

The systematic review (Chapter 2) summarized and critiqued the methods used by researchers or analysts to measure and incorporate family health spillovers in pediatric cost-utility analyses (CUAs) and to measure and integrate the maternal and child health outcomes in maternal-perinatal CUAs. Twenty-nine pediatric CUAs included the family health spillover effects in one or more family members, and forty-five maternal-perinatal CUAs included the health outcomes of both pregnant women and children in their analyses. There was considerable heterogeneity in the methods applied for measuring family health spillover effects and incorporating them into analyses in pediatric CUAs. A similar trend of heterogeneity was observed in the methods used to measure the health outcomes of pregnant women and children and integrate them into maternal-perinatal CUAs. Measurement methods of family health spillover effects included *isolated* and *inherent approaches* to measuring family health spillover effects. In the isolated approach, utility decrements or increments on a parent and/or caregiver due to a child's illness or disabilities were measured. Alternatively, in the inherent approach, the current health state of family members, such as a parent's or caregiver's health utility, reflected the current health-related quality of life (HRQoL) of a parent and, therein, the effects of a child's illness or disabilities on the parent's health was measured.

In addition to using heterogeneous measurement approaches, the pediatric and maternal-perinatal CUAs used a wide array of methods to integrate family health spillovers and the health outcomes of pregnant women and children. The most common approach to include family health spillover effects in the pediatric economic evaluation was to sum the child and parent QALY loss in sensitivity or scenario analysis. In contrast, the most common method in maternal-perinatal CUAs was to sum the pregnant woman and child quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) in the reference case analysis. The review indicated no consensus among researchers on how family health spillover effects should be measured and incorporated into pediatric CUAs, and health outcomes of pregnant women and children should be measured and incorporated into maternal-perinatal CUAs. The heterogeneity in methods and

lack of consensus among researchers reveals the absence of a theoretical framework and health technology assessment (HTA) guidelines on measurement and inclusion of family health spillover effects and health outcomes of pregnant women and children. Only one out of twenty-nine pediatric CUAs used a theoretical framework or theory to justify the methods of inclusion of family health spillover effects.

These findings of inadequate or lack of use of theoretical frameworks or theories to justify various methods used by researchers or analysts for incorporating family health spillover effects reinforced the need to develop a theoretical framework for considering family spillover effects in pediatric CUAs. Although some theoretical frameworks have been proposed to include spillover effects into adult economic evaluations (Basu & Meltzer, 2005), there are important differences between child and adult health that need to be recognized (Keren et al., 2004; Prosser & Wittenberg, 2019a; Ungar, 2009, 2011). As no previous studies have attempted to bring insights and/or evidence from multiple disciplines and conceptualize the relationships between child health and well-being and the family members' health and well-being in the context of pediatric economic evaluation, a theoretical framework was developed in chapter 3 to incorporate family health spillover effects in pediatric CUAs, as described in the following section.

5.1.2 A Theoretical Framework to Incorporating Family Spillover Effects in Pediatric Economic Evaluation

Chapter 3 presented a critical interpretative synthesis (CIS) of sixteen existing theories, conceptual frameworks, and models across the disciplines of psychology, economics, and health services research that support considering family health or cost spillover effects or both in pediatric economic evaluation or that emphasize using a family (or household) level approach in providing care for the child or understanding the child's health and development. Five concepts emerged from the CIS: (a) the health and well-being of family members is interdependent; (b) collective family costs; (c) maximizing the health and well-being; (d) family as a unit of analysis; and (e) factors influencing the child health and development. Building on these five emerging concepts and the relationships among them, a comprehensive *theoretical framework of 'conducting an economic evaluation from a family perspective*' was developed to incorporate family health and cost spillover effects in pediatric CUAs. This proposed theoretical framework posits that conducting an economic evaluation from a family perspective requires considering the

family as a unit of analysis to evaluate the child's health and well-being, where the family costs and consequences related to a child's illness or disability are derived from all family members and incorporated into the analysis of pediatric economic evaluation to evaluate the child's health and well-being with a goal to maximize the family's health and well-being.

Furthermore, based on the above proposed theoretical framework and methods used by researchers to measure and incorporate family spillover effects in included pediatric CUAs in chapter 2, an approach *'conducting pediatric cost-utility analysis from a family perspective'* for incorporating the family health and cost spillover effects in pediatric CUA was presented in chapter 3. The approach to conducting pediatric cost-utility analysis from a family perspective illustrates how a CUA of trial-based pediatric intervention can be operationalized from a family perspective. The proposed approach involves calculating the family costs using an *isolated method* and the family QALYs using an *inherent method*. These proposed methods for calculating family costs and family QALYs were further informed by various methods used by researchers to measure and incorporate family health and cost spillover effects in pediatric CUAs in Chapter 2 and their practical applicability.

An isolated method of estimating family costs would require assessing the cost related to the child's illness or disabilities for each family member separately (items 2 to 9 in Section 3.3.5.1.1, Chapter 3) and summing with the costs of the child's medical or /and non-medical resource use. The family QALYs, in theory, can be estimated using an isolated method, i.e., estimating increments or decrements in utility for each family member due to a child's illness or disabilities (items 2 to 7 in Section 3.3.5.1.2, Chapter 3) and integrating with the child's health utility. However, given the dynamic, complex, and changing dependency relations between a child's health and well-being and parents' health and well-being, estimating increments or decrements on an individual family member's health utility due to a child's adverse health state as isolated quantities can be challenging. Several pediatric and maternal-perinatal CUAs included in Chapter 2 recognized this challenge. Most pediatric CUAs identified in chapter 2 included the spillover disutility of a child's illness (the independent utility loss due to a child member's illness or disability) on family members and caregivers or QALY losses due to a child's illness (the independent QALY loss due to a child member's illness or disability) on family members and caregivers as family health spillover effects. However, they were model-based economic

evaluations, and disutility or QALY losses estimates for family members used in all these studies were primarily derived from three or four previous studies. For instance, out of eleven pediatric CUAs focused on gastroenteritis, nine included family health spillover effects as a caregiver QALY losses. These estimates were derived primarily from one previously published study (Senecal et al., 2006). This speaks to difficulties in applying an isolated approach in measuring and quantifying the family health spillover effects. The challenges of accurately measuring and isolating family health spillover effects from other effects, such a parents' own health is discussed in Chapter 3, Section 3.3.5.1.2. Thus, an alternative method, *an inherent method* for estimating family QALYs was proposed. This involves estimating each family member's health utility, which includes family spillover effects, then estimating QALYs independently and then summing the QALYs of each family member to estimate the family QALYs. The different elements of family costs spillover effects (items 1 to 9 in Section 3.3.5.1.1) and family health spillover effects (items 1 to 7 in Section 3.3.5.1.2) in a three-person household were identified based on a conceptual framework presented in Chapter 1 and methods used by researchers to measure and quantity family cost and health spillover effects in Chapter 2.

5.1.3 Health-Related Quality of life and Mental Health Care Utilization in Parents of Children with Neuroinflammatory Disorders: A Cross-Sectional Study

Informed by the theoretical framework *'conducting an economic evaluation from a family perspective*' and the approach *'conducting the pediatric cost-utility analysis from a family perspective*,' Chapter 4 presented the measurement of the HRQoL and care-related quality of life of parents of children with ND using a cross-sectional data from primary data collection. The mental health service utilization and costs for parents and/or caregivers of children with ND due to a child's illness were also measured. The mean single attribute scores on attributes of emotion and pain were lower than 1.00 (on a scale of 0.00 to 1.00 (Horsman et al., 2003), 0.00=lack of functional capacity, 1.00=full function), indicating some functional impairments in the emotional and physical (pain) well-being of respondent parents. Approximately 49% of the respondent parents reported they experienced some or a lot of problems with their own mental health due to caregiving responsibilities. It is plausible that due to mental stressors caused by caregiving responsibilities, some respondent parents seek mental health services. Approximately 22% (8 out

of 36) of respondent parents in this study indicated they had used mental health services to cope with mental health concerns caused by stress or pressure related to caregiving.

The majority of respondent parents (87.70%; 36 out of 41) and their spouses or partner (80.49%; 33 out of 41) missed paid labour time and/or usual daytime activities to provide care for the affected child. The estimated mean (median; range) annual cost per two parents from a parent payer perspective was CAD 7366 (CAD 2477; CAD 0 to 63077). The productivity cost (paid labour and/or usual daytime activities) of parents and/or caregivers constituted a sizable portion of the overall costs for parents. Overall, the results from this study indicated reduced HRQoL (based on scale '0' dead and '1' perfect health) and care-related quality of life and time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND. Consequently, there are associated costs for the parents and/or caregivers. However, we cannot conclude whether these effects on parents and/or caregivers are due to the child's ND. This study was not able to establish a causal relationship between pediatric ND and impacts on parents' HRQoL, care-related quality of life, and time losses in paid labour and/or usual daytime activities. Results must be interpreted with caution because this study lacked a comparison group of healthy children's parents and/or caregivers, and there were several primary limitations, including potential recall error, a small sample size and costs data that were heavily skewed. Further research with a comparison group of parents and/or caregivers of healthy children and a larger sample is required to determine the family health and cost spillover effects in parents of children with ND.

5.2 Implications

In the following sections, the implications of this thesis for various stakeholder groups are discussed. These stakeholder groups are policy and funding decision-makers, health technology agencies, academic research, healthcare providers, and families of children with chronic illness or disabilities.

5.2.1 Implications for Policy and Funding Decision-Makers in Publicly Funded Healthcare Systems

The CUA is a recommended and established source of value-for-money information for the decision-making process, funding, reimbursement and pricing of a new pharmaceutical product,

technology, or intervention in publicly funded healthcare systems. The Canadian Agency for Drugs and Technologies (CADTH) and the National and Care Excellence (NICE), responsible for providing information on the efficiency of drugs and medical devices to healthcare funding decision-makers across Canada and the UK, require CUAs of alternative treatments or interventions (Canadian Agency for Drugs and Technology in Health (CADTH), 2017). In Canada, CADTH provides recommendations to federal, provincial, and territorial governments on whether or not to cover the cost of medications through their public plans. In addition, some provinces like Ontario, British Columbia and Alberta also have province-specific HTA agencies. For instance, Health Quality Ontario (HQO) in Ontario makes evidence-based recommendations to the Minister of Health and Long-Term Care on which health care services and devices should be publicly funded (Health Quality Ontario, 2022). The HQO's HTA program focuses on the economic evaluation of non-drug health technologies, including medical devices, medical tests, surgical procedures, health care programs, and complex health system interventions.

Many jurisdictions worldwide, including Canada, take a public healthcare payer perspective when making healthcare allocation decisions on how to expend their healthcare budgets. A healthcare perspective neglects a child's health's positive and/or negative effects on family members. The cost of direct healthcare services (e.g., mental health services) used by parents and/or caregivers for their health and well-being as a result of caring for a child with chronic illness or disabilities and covered by the public health payer should be included in a CUA conducted from a publicly funded health care payer perspective but are not typically included. Theoretically, all components of family health and cost spillover effects (see Section 1.3.5.1, Chapter 3) must be included in pediatric CUA from a societal perspective (Drummond et al., 2015). However, only family cost spillover effects, particularly productivity costs of parent(s) due to caregiving and out-of-pocket costs or co-payments of parent(s) for medical and/or non-medical services for the child are usually included (Lavelle et al., 2018). Failure to include these effects in pediatric CUAs might have biased the CUA evidence of treatments or interventions presented to the funding decision-makers and therewith may have led to questionable policy recommendations and suboptimal funding decisions. Limited evidence suggests that the inclusion of family spillover effects in pediatrics CUAs would increase the relative effectiveness of interventions that address conditions with spillover compared to those without spillover effects (Lavelle et al., 2018). Therefore, the current pediatric CUAs, without including family

spillover effects, might have undervalued the true burden of childhood interventions for illnesses. However, there might be circumstances where the inclusion of family spillover effects makes pediatric CUA results not favourable, as described in the theoretical framework chapter 3.

If the public healthcare system aims to maximize health gain across all populations from available healthcare resources, the policy and funding decision-makers should ask the HTA agencies, such as CADTH and HQO, to consider the family spillover effects in pediatric CUAs. This thesis explored the relationship between child health and well-being and the family members' health and well-being using insights from several disciplines and presented a theoretical framework for considering family spillover effects in pediatric economic evaluation. The funding decision-makers at the federal and/or province level could encourage the HTA agencies to use the proposed theoretical framework and approach to conduct the pediatric CUAs from a family perspective methodological approach to inform the methodologies for measuring and including the family spillover effects.

Moreover, the parents of children with ND reported lower HRQoL (based on scale ‘0’ dead and ‘1’ perfect health) and care-related quality of life and missed paid labour and/or usual activities. We were unable to conclude the family health and cost spillover effects of pediatric ND on parents and/or caregivers. Other researchers' systematic reviews and meta-analyses have concluded that having a child with chronic illness or disabilities, including MS, a type of ND, impacts family members' mental health and economic well-being (Boettcher et al., 2021; Cohn et al., 2020; O. Ernstsson et al., 2016). The results from this study and other studies could be used to inform policymaking for parents and/or caregivers of children with chronic illness and disabilities. Providing financial support or access to mental interventions that alleviate the mental stress of families is critical. The federal and provincial government policymakers should develop policies to target parents and caregivers from marginalized and vulnerable groups such as new immigrants, indigenous communities, and rural communities that endure significant effects (Banks & Miller, 2005; Bronheim, Soto, & Anthony, 2015; King et al., 2011). The Canadian federal government has the Child Disability Benefit (an annual maximum of CAD 2915 in 2022) for low- and modest-income parents with children with severe disabilities. This amount could be raised to sufficiently meet the needs of a child with disabilities and their families (Government of Canada, 2022). Psychologists, social workers, and other types of therapists are not covered under

Ontario Health Insurance Plan (OHIP). Some respondent parents and/or caregivers and their spouses or partners reported using these services in the cross-sectional study. Expanding OHIP coverage to include universal mental health care may reduce barriers to access to mental health services for parents and/or caregivers.

5.2.2 Implications for Health Technology Agencies

The findings from this thesis have particular relevance for HTA agencies that set guidelines for conducting economic evaluation and provide evidence on cost and effectiveness to decision-makers to help them determine whether to publicly fund select health technologies. A theoretical framework to incorporate family health spillover effects in the pediatric economic evaluation was presented in the theoretical framework chapter 3. The theoretical framework asserts that child health and development and family members' health and well-being are intertwined. Individual members exercise continuous and reciprocal influences on one another. Therefore, a child's health and well-being are inextricably embedded in the family unit and can never be fully understood independently of that unit. The HTA agency using information from this theoretical framework could encourage analyses and researchers to incorporate the family spillover effects in pediatric economic evaluation. Systematic review chapter 2 showed that researchers and analysts used various methods to measure and include family health spillover effects in pediatric and maternal-perinatal CUAs. These inconsistent methods might have biased the CUA results leading to poor policymaking. For instance, although the inclusion of family health spillover effects in NICE appraisals is uncommon, this review found that five NICE appraisals incorporated family health spillover effects. The methods used to measure and include family health spillover effects in these appraisals were not similar. Such inconsistency makes the results less comparable and might provide poor information to decision-makers regarding the effectiveness of alternatives. Having a standard framework or guidelines on including family spillover effects would eliminate such biases and poor decision-making.

The CADTH, a Canadian national organization, produces and disseminates a guideline for Canada's economic evaluation of health technologies (Canadian Agency for Drugs and Technology in Health (CADTH), 2017). Industry sponsors (such as pharmaceutical industry sponsors or other agencies, manufacturers, suppliers, and distributors) must follow the CADTH

guidelines when applying for reimbursement review of new pharmaceutical products, technology, or intervention. These guidelines are updated periodically to produce credible and standardized economic information that is relevant and useful to decision-makers in Canada's public health care system. In their future guidelines update, HTA agencies could recommend and/or make an explicit requirement for the agencies to include family spillover effects in pediatric CUAs in reports they need to submit for drug approval and reimbursement. One way to move forward is by establishing a separate reference case *'family perspective'* methodological approach for fully incorporating family spillovers in pediatric CUAs and making an explicit requirement to include both the family cost and health spillover effects in analyses or provide valid justifications for not including family health and cost spillover effects. The current CADTH guideline recommends incorporating the productivity cost (paid labour and/or usual daytime activities) of parents and/or caregivers in a non-reference case from a societal perspective (Canadian Agency for Drugs and Technology in Health (CADTH), 2017). National HTA agencies, such as CADTH, could also encourage sponsor agencies to conduct a separate systematic review as part of HTA package on the costs and benefits (HRQoL or others) of the child's health technology under review for family members.

CADTH recommendations are generally used by all Canadian provinces. However, the health care funding decision-makers of individual Canadian provinces are not obligated to follow CADTH recommendations. Ontario for example, has its own an independent agency, HQO, that makes make evidence-based recommendations to the Ministry of Health on which health care services and devices should be publicly funded. The Ontario Health Technology Advisory Committee (OHTAC), a committee within the HQO, produces HTA reports that analyze available evidence on clinical benefit, value for money, and patient preferences and values (Health Quality Ontario, 2022). Health economists could use the proposed theoretical framework to develop approaches to include the family health and costs spillover effects in pediatric economic evaluations. Furthermore, items listed in Section 1.3.5.1.2, the theoretical framework chapter 3 could inform the health economists or analysts working on HTA agencies on how to measure and quantity family costs and health spillover effects related to pediatric illness or disabilities. Furthermore, systematic review chapter 2 summarized the methods used by researchers to measure, value, and incorporate the family health spillover effects and integrate

the health outcomes of pregnant women and children. Health economists or analysts working at HTA agencies, such as OHTAC, can use findings from this review to inform their future methods of measurement, valuation, and incorporation of family health spillover effects in pediatric CUAs. Moreover, in systematic review chapter 2, we have extracted and listed estimates of disutilities related to caregiving of parents and family members for the child with various chronic illnesses or disabilities. These estimates could be used in model-based pediatric CUAs to incorporate the family health spillover effects.

5.2.3 Implications for Academic Research

The findings from this thesis have particular implications for researchers working in academic settings. One of the commonly noted reasons for excluding spillover effects in economic evaluation, including pediatric economic evaluation, was the lack of a theoretical framework for the inclusion of spillover effects (J.M. Tilford & N. Payakachat, 2015; E. Wittenberg, L. P. James, & L. A. Prosser, 2019). This thesis closes that gap and presents a theoretical framework for conducting an economic evaluation from a family perspective. This may encourage researchers or analysts working in academic settings to explore empirical methods based on the proposed theoretical framework for including family spillover effects in pediatric CUAs. This could potentially lead to rigorous and standardized methods for measuring, valuing, and incorporating family health spillover effects in pediatric CUAs. Furthermore, systematic review chapter 2 of the thesis included a comprehensive review of methods used by researchers to measure and incorporate family health spillover effects. This information could be helpful for researchers to develop further methods of measuring and incorporating the family health spillover effects in economic evaluation.

5.2.4 Implications for Health Care Providers

The results from the cross-sectional indicated reduced HRQoL, care-related quality of life and time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND. Healthcare providers, including pediatricians, pediatric neurologists, family physicians, and others involved in the child's care, can coordinate with mental health services providers, such as psychologists, social workers, and mental health counsellors, for psychological support to parents and caregivers. The time of a diagnosis is a critical component that needs to be

considered. Research on other childhood diseases or disabilities has shown greater psychological distress at the beginning of diagnosis and declined over time (Boman et al., 2003; Brehaut et al., 2011; Okado, Tillery, Howard Sharp, Long, & Phipps, 2016; Stuart & McGrew, 2009). This could be due to a lack of knowledge of parents and/or caregivers about childhood diseases, such as further diagnosis, prognosis, and short and long-term impacts. Furthermore, children may need a wide range of specialized services, often including education, social services, and health services. Finding services to meet these needs, determining eligibility, and deciding who will pay for them can be stressful for parents. Pediatric healthcare providers can help to reduce parental stress by providing parents with information regarding the child's ND and directing them towards appropriate services or healthcare providers who can assist them in getting access to the appropriate services, such as social workers, particularly at the time of diagnosis. The needs of parents and caregivers are often overlooked in efforts to provide the best care for the patient. Simply asking the parents or/caregivers about their health and well-being during the clinic visit for their child might alleviate the stress on parents and/or caregivers. During the data collection for the empiric study Chapter 4, I had several instances where parents and/or caregivers were emotional when I asked, "During the past week, have you been feeling happy or unhappy,"? (HUI questionnaire). For instance, one of the parents paused and cried on the phone. The parent said, "I know my child is going through too much, but I am exhausted. We saw the family physician, neurologist, social worker, and others care providers for my child; no one asked me 'how I was feeling.' Thank you for asking and doing this study.'

5.2.5 Implications for Families of Children with Chronic Illness or Disabilities

In public health policymaking, acknowledging the positive and negative impacts of a child's illness or disabilities on family welfare will benefit patients, families, friends, and society. The results of the reduced HRQoL, carer-related quality of life and missed paid labour and/or usual activities might inform parents and/or caregivers to receive the appropriate and timely mental health treatments or support for their emotional stress related to caregiving. Furthermore, for parents and/or caregivers, the results of this study can provide information in their advocacy effort in conjunction with patient and caregiver organizations, such as the MS Society of Canada, Autism Speaks Canada, and Ontario Caregiver Organization, with federal and provincial

governments in advocating for timely and appropriate financial supports and treatments for mental health of parents and/or caregivers. The majority of respondent parents reported that they and their spouses or partners missed paid labour time and/or usual daytime activities to provide care for the affected child. Also, respondent parents reported reduced HRQoL and carer-related quality of life. Although due to a lack of control group we were unable to conclude definitively that these are family spillover effects on parents and/or caregivers due to the child's ND, this evidence can use to advocate for timely supports for parents and/or caregivers. Moreover, the systematic review chapter 2 revealed that only a few pediatric CUAs had incorporated family health spillover effects. Parents and/or caregivers, in conjunction with patient and caregiver organizations, can advocate for the inclusion of family spillover effects in pediatric CUAs.

CADTH accepts inputs from patient groups (individual patients or caregivers when there is no patient advocacy group representing patients with a condition for which the technology is under review) in the drug reimbursement review process. Patient group input includes patients' experiences and perspectives of living with a medical condition for which an intervention under review is indicated, their experiences with currently available treatments, and their expectations for the intervention under review. Likewise, OHTAC conducts a (direct) patient engagement to assess the value of obtaining information about the preferences and values of people with lived experience of the health condition and health technology being reviewed. Direct patient engagement activities include in-person or telephone interviews, focus groups, or surveys. In these direct engagement activities, patients can advocate considering the impacts parents and/or caregivers them on pediatric CUAs.

5.3 Future Research

The findings of this thesis present several opportunities for future research—detailed descriptions of further research related to each objective can be found in individual chapters. The following paragraphs highlight some of the potential opportunities.

The magnitude of the costs and family health spillover effects on family members may depend on the nature and severity of a child's disease or conditions (Cohn et al., 2020; Lamsal & Zwicker, 2017; E. Wittenberg et al., 2019). Some childhood conditions such as cerebral palsy, spina bifida, cystic fibrosis and epilepsy can have significant health and well-being and financial

consequences for family members compared to others. This hypothesis needs to be tested empirically. It might not be feasible or desirable for all pediatric CUAs to incorporate the family health spillover effects. Therefore, future research must investigate and identify the childhood conditions that produce substantial spillover effects on family members. Currently, studies comparing health outcomes of parents of chronically ill children with parents of healthy children are limited (Cohn et al., 2020; E. Wittenberg et al., 2019). Much more work can be expected in this area in the future, allowing for the comparison of family spillover effects on family members across childhood illnesses or disabilities.

Accurate and valid measurement of family health spillover effects and the health outcomes of pregnant women and children is an essential prerequisite to incorporating these effects in CUAs. To able to be used in the CUA, the recommended type of economic evaluation, the family health spillover effects should be measured using preference-based instruments or direct measurement approaches such as time-trade-off and standard gamble (SG) (Drummond et al., 2015). These preference-based instruments are developed to measure the HRQoL of life of patients, and domains included in these instruments may not adequately capture components of HRQoL most relevant to caregivers and family members. Some new instruments, such as CarerQol, include domains beyond typical HRQoL (W. Brouwer, J. Van Exel, B. Van Gorp, & W. Redekop, 2006a). While they may accurately capture caregiver-relevant dimensions, their valuations are based on the care-related quality of life and are different from the traditional preference-based instrument HRQoL. Therefore, integrating CarerQol utility scores with child utilities could be difficult. Future researchers should strive to validate existing approaches or develop novel approaches to measure, assess, value, and incorporate the health effects on family members. Moreover, new instruments must explore other dimensions of family health spillover effects on family members. For instance, research has shown that having a sibling with chronic illness or disability impacts the health and well-being of unaffected siblings. Seeing the changes in the health of an unaffected child due to the illness of an affected child might impact the parent's health and well-being (Lamsal & Ungar, 2021; Sharpe & Rossiter, 2002). These health and well-being effects must be measured as family health spillover effects and/or included in the pediatric CUA.

In this thesis a theoretical framework for '*conducting economic evaluation from a family perspective*' was developed. Empirical studies are warranted to test the validity of hypothesized inter-relationships among proposed synthesized constructs and concepts in the proposed theoretical framework. For instance, our proposed theoretical framework posits that the health and well-being of the child and family members are interdependent. Therefore, the decision to invest in the child's health and well-being is made by parents considering the health-well-being of all family members. It would be important in future studies to collect empirical data on the health outcomes of the child and family members and the healthcare costs of a child's illness for the parents and evaluate the relationships between the health outcomes and healthcare costs for parents at the various stages of a child's disease. Furthermore, the proposed theoretical framework posits that the parents reduce spending on market goods and services and allocate funding towards treatments for this child. In taking forward the impact of a child's illness on parents' spending, it will be important to collect the data on the cost of household goods, medical and non-medical service costs of a child's condition for parents, and the health and well-being of the child. This might allow researchers to examine the impacts of a child's illness on parents' spending on household goods. Future studies can also explore the feasibility of the proposed approach of conducting pediatric CUA from a family perspective in trial-based CUAs. For example, future trial-based pediatric economic evaluation could measure and estimate the family cost using an isolated method as described in sections 3.3.5.1.1 and 3.3.5.1.3 in the theoretical framework and measure and estimate the family QALYs as described in sections 3.3.5.1.2 and 3.3.5.1.3 of two alternative interventions and treatments. The differential average total cost per QALY and differential mean QALYs per family can be estimated. These results could be presented to funding decision-makers in publicly funded healthcare systems to assist on whether or not to cover the cost of medications through their public plans.

In this thesis, we develop a theoretical framework for conducting pediatric economic evaluation from a family perspective and present an approach of the proposed approach of conducting pediatric CUA from a family perspective. The methodology for integrating family health spillovers effects into analyses is still developing. Further work is needed to develop empirical methods or approaches to incorporate the spillover effects into economic evaluations. The proposed theoretical framework could be used to develop other approaches to measuring and

integrating the health outcomes and costs of the child and family members and conduct the pediatric economic evaluation from the family perspective. Therefore, funding decision-makers and policymakers could be better informed regarding the costs and effectiveness of alternative pediatric treatments or interventions being compared. For instance, one potential exploration approach could be mathematically combining the health utilities of the child and all family members to estimate the family QALYs. Finally, another area of needed research informed by this thesis is measuring family cost and health spillover effects for parents of children with ND. In an empiric study Chapter 4, we could not establish the causal relationship between a pediatric ND and family spillover effects due to the lack of a control group of parents of healthy children. Longitudinal prospective cohort studies with a large sample size and control group of parents of healthy children are warranted to measure the impacts of children's ND on parents' health and well-being and economic well-being. Furthermore, as described in Chapter 1 section 1.2.3.4 and Chapter 3, several internal and external factors such as parents' own health, the health and well-being of other family members, and socioeconomic characteristics impact the parents' and/or caregivers' health and well-being. Future studies must aim to control the influence of these factors and use appropriate statistical methods on parents' health and well-being to get unbiased estimates of family health and cost spillover effects on parents of children with ND.

We also believe that the results of this thesis could be expanded to areas of health services search. For example, one potential use of the proposed theoretical framework is in the economic evaluation of cascade genetic testing in relatives of people known to possess genetic variants that cause hereditary cancers or other diseases (Cernat et al., 2021). Cascade testing may improve the health and well-being of other family members by facilitating the implementation of prevention strategies such as surveillance and (management) treatments that can reduce morbidity and mortality in these individuals who share the same disease-causing gene variants. However, cascade costs and health effects are not usually included in the economic evaluation of genetic testing. Another potential use is measuring, assessing, and incorporating spillover effects in the economic assessment of adult health intervention. Adults with diseases such as Alzheimer's or other chronic disabilities may require comprehensive care for activities such as feeding, bathing, dressing, and transportation (Brodaty & Donkin, 2022). Informal caregiving can impact the health and well-being of family members, and these effects are often not included in economic

evaluation (Brodaty & Donkin, 2022; Mittelman, Roth, Clay, & Haley, 2007; Martin Pinquart & Sörensen, 2006; E. Wittenberg et al., 2019).

5.4 Conclusion

Childhood illness or disability can positively and negatively affect family members and/or caregivers' health and well-being and economic well-being. This has been recognized for some time. Yet, the current approach in pediatric economic evaluation treats patients as isolated individuals, ignoring the potential effects of their illness on family members. If considered, these effects on family members and/or caregivers may influence the cost-effectiveness results and hence, resource allocation decisions. The lack of a theoretical framework and a standard approach to measuring and incorporating into pediatric CUA has hindered attempts to include the family spillover effects. This thesis has developed a theoretical framework *'conducting economic evaluation from a family perspective'* using insights from the theories, frameworks and models that support the reasons why family spillover effects should be considered in pediatric economic evaluation or emphasize using a family-level approach in understanding the child's health and development. Informed by the proposed theoretical framework, this thesis examined the HRQoL, caregiver quality of life, and costs for parents of children with ND. The findings indicated reduced HRQoL(based on scale ‘0’ dead and ‘1’ perfect health), carer-related quality of life, time devoted to paid labour and/or usual activities of parents and/or caregivers of children with ND. These data are limited by their cross-sectional data. Our lack of longitudinal data and a control population limits the ability to draw definitive conclusions regarding spillover effects in this population. Altogether, this thesis aimed to advance understanding of the family spillover effects of a child's illness or disability and has contributed to the theoretical and methodological development of considering these effects in pediatric economic evaluation. Future research should continue to advance our knowledge of family spillover effects and primarily focus on advancing methodology to measure and incorporate these effects that will enable systematic inclusion into pediatric economic evaluations.

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em+for+a+new+preference-based+measure+of+health-related+quality+of+life+for+children.&aulast=Stevens&pid=%3Cauthor%3EStevens+K%3C%2Fauthor%3E%3CAN%3E19693703%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E

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Appendices

Appendix A Medline Search Strategy Used in the Systematic Review of Pediatric and Maternal-Perinatal Cost-utility Analyses

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:

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1 "cost allocation"/ or cost-benefit analysis/ or exp "cost control"/ or exp health care costs/ or exp health expenditures/ or economics, dental/ or economics, hospital/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp Technology Assessment, Biomedical/ or exp Health Services Research/ or exp "Health Services Needs and Demand"/ or Quality Adjusted Life Years/ or Delivery of Health Care/ or "Length of Stay"/ or Primary Health Care/ (514494)
2 ("decision analy*" or "decision model*").ab,ti. (9837)
3 1 or 2 (519519)
4 ("economic evaluation$" or "cost effectiveness" or "cost-effectiveness" or "cost utilit$" or "cost-utilit$" or "economic assessment" or QALY or cost$ or "quality adjusted life year$" or HYE or "health year equivalent" or "willingness to pay" or "willingness-to-pay" or "contingent valuation" or "net health benefit" or "net monetary benefit" or "acceptability curve$" or "cost-acceptability curve$" or "cost acceptability curve$").ab,ti. (630463)
5 3 and 4 (134495)
6 (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or preschool* or pre-school* or

kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc*).ab,ti. (2644767)
7 5 and 6 (14094)
8 limit 5 to ("adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (50371)
9 (baby or babies or kid or kids or youth$ or child$ or adolescent$ or teen$ or pediatric$ or paediatric$ or infant$ or infancy or newborn$ or neonate$ or student$ or youth).ab,ti. (2436348)
10 8 and 9 (3913)
11 7 or 10 (14499)
12 fetus/ or prenatal care/ or exp prenatal diagnosis/ or pregnancy outcome/ or Congenital Abnormalities/ (242791)
13 5 and 12 (1292)
14 11 or 13 (15069)
15 limit 14 to (address or autobiography or bibliography or biography or comment or congress or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or festschrift or historical article or interview or lecture or legal case or letter or news or overall or periodical index or retracted publication or "retraction of publication") (322)
16 14 not 15 (14747)
17 exp animals/ not humans.sh. (4756396)
18 16 not 17 (14726)
19 limit 18 to yr="1980 -11/16/2020" (14569)
20 limit 19 to English language (13908)

Appendix B Medline Search Strategy Used in the Scoping Review of Theories, Framework and Conceptual Model

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present (09-11-2020)>
Search Strategy:

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1 *Models, Theoretical/ (61322)
2 (theor* or framework* or concept*).tw,kf. (1300886)
3 1 or 2 (1342955)
4 *Infant/ (1732)
5 (infant* or infancy or new-born* or baby* or babies or neonat*).tw,kf. (727045)
6 *Child/ (3413)
7 (child* or kid or kids or toddler*).tw,kf. (1452036)
8 *Adolescent/ (5543)
9 (adoles* or teen* or boy* or girl*).tw,kf. (517893)
10 *Pediatrics/ (38311)
11 (paediatric* or pediatric*).tw,kf. (372547)
12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (2365240)
13 *Family Health/ (7515)
14 *Caregivers/ (25603)
15 *Cost-Benefit Analysis/ (9123)
16 ("family effect" or "spillover effect" or "health spillover" or "cost spillover" or "indirect cost" or "caregiver effect" or "informal care").tw,kf. (3356)
17 ("family health" or "household effect" or "household production" or "family utility" or "family system").tw,kf. (7345)
18 13 or 14 or 15 or 16 or 17 (50583)
19 3 and 12 and 18 (1457)
20 limit 19 to English language (1353)

Appendix C Quality of Health Economic Studies (QHES) Instrument

	Questions	Points	Yes	No
1.	Was the study objective presented in a clear, specific, and measurable manner?	7		
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3.	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1		
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6.	Was incremental analysis performed between alternatives for resources and costs?	6		
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	6		
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15.	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16.	Was there a statement disclosing the source of funding for the study?	3		
	TOTAL POINTS	100		

Appendix D Characteristics of Pediatric Cost-utility Analyses Including Family Health Spillover Effects

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
Infectious or parasitic diseases (n=15)						
Bilcke et al., 2009	Belgium	Gastroenteritis	Cohort of newborn	To estimate the cost-effectiveness of universal childhood rotavirus vaccination	(i) Publicly funded healthcare system; societal (ii) Seven years	(i) Universal rotavirus (Rotarix® or RotaTeq®) vaccination (ii) No vaccination
Chodick et al., 2009	Israel	Gastroenteritis	Birth cohort of 143,500 children	To investigate the cost-effectiveness of vaccinating an Israeli birth cohort	(i) Healthcare system; societal (ii) Five years	(i) Rotavirus (Rotarix® or RotaTeq®) vaccination (ii) No vaccination
Coyle et al., 2012	Canada	Gastroenteritis	Birth cohort of 354,617children	To assess the cost-effectiveness of rotavirus vaccination of infants	(i) Healthcare system; societal (ii) Five years	(i) Rotavirus (RotaTeq®or Rotarix®) vaccination (ii) No vaccination
Hansen Edwards et al., 2017	Norway	Gastroenteritis	Children aged 0 to four years	To estimate cost-effectiveness and effects of childhood rotavirus	(i) Healthcare system; societal (ii) Five years	(i) Universal rotavirus (Two-dose of Rotarix® or three dose of Rota Teq®) vaccination (ii) No vaccination

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				vaccination in Norway		
Jit & Edmunds, 2007	United Kingdom	Gastroenteritis	Hypothetical cohort of children from birth to five years of age	To evaluate the cost-effectiveness of an immunization programme using a model that followed imaginary cohorts of children in England and Wales from birth to five years of age	(i) Healthcare system; societal (ii) Lifetime	(i) Rotavirus (RotaTeq® or Rotarix®) vaccination (ii) No vaccination
Melliez et al., 2008	France	Gastroenteritis	Hypothetical cohort of birth cohort of 750,000 children	To assess the effectiveness and cost-effectiveness of routine childhood vaccination by new vaccines against rotavirus in France	(i) Societal (ii) Three years	(i) Rotavirus vaccination (ii) No vaccination
Milne et al., 2009	New Zealand	Gastroenteritis	Children aged 0 to four years	To estimate the cost-effectiveness of	(i) Healthcare system; patients; societal	(i) Rotavirus vaccination (ii) No vaccination

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				incorporating a pentavalent rotavirus vaccine into the national immunization schedule	(ii) Five years	
Newall et al., 2007	Australia	Gastroenteritis	Hypothetical cohort of children	To estimate the cost-effectiveness of the two registered rotavirus vaccines.	(i) Healthcare system; societal (ii) Five years	(i) Rotavirus (RotaTeq® or Rotarix®) vaccination (ii) No vaccination
Shim & Galvani, 2009	United States	Gastroenteritis	Children aged 0 to four years	To estimate the cost-effectiveness of mass vaccination of US infants with the recently available rotavirus vaccine, RotaTeq®	(i) Healthcare system; societal (ii) Five years	(i) Rotavirus vaccination (ii) No vaccination
Tilson et al., 2011	Ireland	Gastroenteritis	Children aged under 36 months	To evaluate the cost-effectiveness of universal infant rotavirus	(i) Healthcare system; societal (ii) Five years	(i) Universal Rotavirus (Rotarix® or RotaTeq®) vaccination

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				vaccination compared to the current standard of care of no vaccination		(ii) No vaccination
Tu et al., 2012	Vietnam	Gastroenteritis	Birth cohort of 1,485,000 children	To assess the cost-effectiveness of rotavirus immunization in Vietnam	(i) Healthcare system; societal (ii) Five years	(i) Universal rotavirus vaccination (ii) No vaccination
Christensen et al., 2014	United Kingdom	Invasive meningococcal group B	Birth cohort of children	To use mathematical and economic models to predict vaccination's epidemiological and economic impact	(i) NHS; PSS (ii) Lifetime	(i) Vaccination with Bexsero (ii) No vaccination
Tu et al., 2014	Canada	Invasive Neisseria meningitidis serogroup B (MenB)	Hypothetical birth cohort of 150,000	To assess the cost-effectiveness of a novel MenB vaccine	(i) Healthcare system (ii) Lifetime	(i) A novel MenB vaccination (ii) No vaccination
Prosser et al., 2011	United States	Influenza	Hypothetical cohort of children aged 6 months to 4 years	To evaluate the cost effectiveness of live attenuated influenza	(i) Societal perspective (ii) NS	(i) Live attenuated influenza vaccine (ii) No vaccination

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				vaccine using new data on adverse events		
Bilcke et al., 2013	Belgium	Varicella	Birth cohort of 125,000 children	To assess the effectiveness and cost-effectiveness of a universal childhood varicella-zoster vaccination program	(iii) Healthcare system (iv) Lifetime	(iii) Universal childhood varicella-zoster vaccination (iv) No universal vaccination
Diseases of the blood or blood-forming organs (n=1)						
NICE HST7, 2018	United Kingdom	Adenosine-deaminase deficiency-severe combined immunodeficiency (ADA-SCID)	Children aged one year	To estimate the cost-effectiveness of strimvelis for treating ADA-SCID	(i) NHS (ii) Lifetime	(i) Strimvelis (ii) Haematopoietic stem cell transplants
Endocrine, nutritional, or metabolic disorders (n=2)						
NICE HST2, 2015	United Kingdom	Mucopolysaccharidosis type IVa	Children	To conduct an economic evaluation of elosufase alfa	(i) NHS and PSS perspective (ii) Lifetime	(i) Elosulfase alfa (ii) Established clinical management
NICE HST8, 2018	United Kingdom	X-linked hypophosphatemia	Children aged one to 12 years	To conduct an economic evaluation of burosumab compared to	(i) NHS (ii) 16 years in girls and 17 years in boys	(i) Burosumab (ii) Conventional therapy

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				conventional therapy		
Mental, behavioural, or neurodevelopmental disorders (n=5)						
Chatterton et al., 2019	Australia	Anxiety disorder	Children aged 7 to 17 years	To estimate the cost-effectiveness of stepped care for the treatment of anxiety disorder in children	(i) Healthcare system; societal (ii) 12 months	(i) Stepped care (ii) Manualized treatment
Creswell et al., 2015	United Kingdom	Anxiety disorder	Children aged 7 to 12 years	To assess the cost-effectiveness of the cognitive–behavioural therapy (CCBT) + maternal cognitive–behavioural therapy (MCBT) and CCBT + mother–child interactions (MCI) treatment arms compared with the CCBT treatment arm	(i) Healthcare system; societal (ii) 12 months	(i) CCBT+MCBT; CCBT+MIC (ii) CCBT
Schawo et al., 2015	The Netherlands	Attention deficit hyperactivity disorder	Children and adolescents	To evaluate the cost-	(i) Societal (ii) 12 years	(i) OROS (ii) IR

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				effectiveness of methylphenidate osmotic-release oral system (OROS) compared with methylphenidate immediate-release (IR) for patients with suboptimal response to IR		
Tubeuf et al., 2019	United Kingdom	Self-harm	Children aged 11–17 years	To present alternative parental health spillover quantification methods in the context of a randomized controlled trial and discuss the limitations of those methods.	(i) NS (ii) 12 months	(i) Self-harm intervention: Family therapy (ii) Treatment as usual

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
Ulfsdotter et al.,2015	Sweden	Behavior problems	Children aged between three to 12 years	To conduct a cost-effectiveness analysis of the universal parenting program All Children in Focus (the ABC programs)	(i) Societal (ii) Three months	(i) The ABC programs (ii) Usual care
Disease of the nervous system (n=2)						
de Kinderen et al., 2016	The Netherlands	Intractable epilepsy	Children aged between one to 18 years	To conduct cost-effectiveness of the ketogenic (KD) diet compared with care as usual (CAU) in children and adolescents with intractable epilepsy	(i) Societal (ii) Four months	(i) Ketogenic diet (ii) Care as usual
NICE, HST3, 2016	United Kingdom	Duchene muscular dystrophy	Children	To conduct and economic evaluation of Ataluren for treating Duchene	(i) NHS and PSS (ii) Lifetime	(i) Ataluren (ii) Standard care

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
				muscular dystrophy		
Diseases of the ear or mastoid process (n=2)						
O'Brien et al., 2009	United States	Otitis Media	Birth cohort of children	To evaluate the cost-effectiveness of current and candidate vaccines against otitis media.	(i) Societal (ii) Lifetime	(i) Vaccination against Otitis media (ii) No vaccination
Prosser et al., 2004	United States	Otitis media and other diseases	Children aged between zero to 18 years	To measure parents' and other adults' values for preventing disease associated with pneumococcal infection and to evaluate how including these values changes the economic appraisal of pneumococcal conjugate vaccine.	(i) Societal (ii) NS	(i) Pneumococcal Conjugate Vaccine (ii) No vaccine
Diseases of musculoskeletal system or connective tissue (n=1)						

Author, Year of publication	Country of population	Disease/Condition	Participants	Aim/Objective	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator
NICE, TA373, 2015	United Kingdom	Juvenile idiopathic arthritis	Children aged 12 years	To conduct an economic evaluation of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis	(i) NHS (ii) 6 years	Compared among abatacept, adalimumab, etanercept and tocilizumab
Certain conditions originating in the perinatal period (n=1)						
Partridge et al., 2015	United States	Resuscitation	Infants born at 23 weeks of gestation	To investigate the cost-effectiveness of resuscitation of infants born 23 0/7–23 6/7 weeks' gestation.	(i) Maternal–neonatal (ii) NS	(i) Resuscitation (ii) No resuscitation

NICE: National Institute for Health and Care Excellence; HST: highly specialized technologies; TA: technology appraisal; NHS: National Health Service; PSS: personal social services; NS: not stated.

Appendix E Characteristics of Maternal-perinatal Cost-utility Analyses Including Health Outcomes of the Mother and Child

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
Congenital maternal heart disease affecting fetus or newborn (n=2)							
Bak et al., 2020	United States	Screening for congenital heart disease	Pregnant women and children	To perform a cost-effectiveness analysis of different follow-up strategies for non-obese and obese women who had an incomplete fetal cardiac screening for major congenital heart disease	Fetuses	(i) Healthcare system (ii) Lifetime	Five strategies : (1) no follow-up ultrasound (US) examination but direct referral to fetal echocardiography (FE); (2) one follow-up US, then FE if fetal cardiac views were still suboptimal; (3) up to two follow-up US, then FE if fetal cardiac views were still suboptimal; (4) one follow-up US and no FE; and (5) up to two follow-up US and no FE were compared in non-obese, obese and

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
							Class-III-obese women.
Mistry et al., 2013	United Kingdom	Screening for congenital heart disease	Pregnant women and children	To estimate the longer-term cost-effectiveness of using telemedicine screening for prenatal detection of congenital heart disease	Fetuses	(i) Healthcare system (ii) Lifetime	(i) Telemedicine screening (ii) No screening
Disease of the circulatory system (n=1)							
Clennon et al., 2021	United States	Eisenmenger syndrome	Pregnant women and children	To compare costs and outcomes of pregnancy in women with Eisenmenger syndrome to the use of gestational surrogates in their pregnancies	Pregnant women	(i) NS (ii) Lifetime	(i) Gestational surrogates (ii) No surrogates
Diseases of appendix (n=1)							
Kastenberg et al., 2013	United States	Acute appendicitis	Pregnant women and children	To assess the cost-effectiveness of diagnostic laparoscopy, computed tomography and	Pregnant women	(i) Societal (ii) Lifetime	(i) Computed tomography (ii) Magnetic resonance imaging

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				magnetic resonance imaging following indeterminate ultrasound in pregnant women with suspected appendicitis			
Delivery (n=6)							
Chung et al., 2001	United States	Methods of delivery	Pregnant women and children	To evaluate whether it is cost-effective for women with a history of a prior caesarean delivery to undergo a trial of labor	Pregnant women	(i) Societal (ii) Lifetime	(i) Trial of labor (ii) Elective repeat caesarean delivery
Gilbert et al., 2013a	United States	Methods of delivery	Pregnant women and children	To estimate the cost-effectiveness of a trial of labor after one previous caesarean when incorporating long-term events and outcomes	Pregnant women	(i) Societal (ii) Lifetime	(i) Trail of labor after one previous caesarean delivery (ii) Elective repeat caesarean delivery
Gilbert et al., 2013b	United States	Methods of delivery	Pregnant women and children	To estimate the cost-effectiveness of a trial of labor	Pregnant women	(i) Societal (ii) Lifetime	(i) Trial of labor after one previous caesarean delivery

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				after one previous caesarean delivery			(ii) Elective repeat caesarean delivery
Kaimal et al., 2011	United States	Methods of delivery	Pregnant women and children	To investigate the cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women	Pregnant women	(i) Societal (ii) Lifetime	(i) Expectant management (ii) Induction of labor
Tan et al., 2010	United States	Methods of delivery	Pregnant women and children	To determine the incremental cost-effectiveness ratio of External cephalic version compared to scheduled caesarean for term breech presentation	Pregnant women	(i) Societal (ii) 12 weeks after delivery	(i) External cephalic version trial (ii) A scheduled caesarean for a breech presentation
Wymer et al., 2014	United States	Methods of delivery	Pregnant women and children	The purpose of this study was to estimate costs and outcomes of subsequent trials of labor after caesarean delivery compared with	Pregnant women	(i) Healthcare system (ii) Lifetime	(i) Trial of labor after one previous caesarean delivery (ii) Elective repeat caesarean delivery

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				elective repeat caesarean deliveries			
Diabetes mellitus in pregnancy (n=6)							
Chen et al., 2016	Singapore	Screening for gestational diabetes mellitus	Pregnant women and children	To conduct an incremental cost-effectiveness analysis from the payer's perspective in Singapore of 3 gestational diabetes mellitus screening strategies: universal, targeted, or no screening.	Pregnant women and fetuses	(i) Healthcare system (ii) Lifetime	(i) Universal and targeted screening for gestational diabetes mellitus (ii) No Screening
Danyliv et al., 2016	Ireland	Screening for gestational diabetes mellitus	Pregnant women and children	To assess the cost-effectiveness of screening for gestational diabetes mellitus in primary and secondary care settings, compared with a no-screening option.	Pregnant women and perinates	(i) Healthcare system (ii) Lifetime	(i) Screening for gestational diabetes mellitus (ii) No screening

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
Farrar et al., 2016	United Kingdom	Screening for hyperglycaemia /Gestational diabetes	Pregnant women and children	To evaluate the cost-effectiveness of alternative strategies of combined screening, diagnosis, and treatment of hyperglycaemia during pregnancy	Pregnant women and perinates	(i) National health service (NHS); personal social services (PSS) (ii) Three months	(i) Screen only, Universal diagnostic test, Screen, and diagnostic test (ii) No screening/testing or treatment
Ohno et al., 2011	United States	Gestational diabetes mellitus	Pregnant women and children	To investigate the cost-effectiveness of treating mild gestational diabetes mellitus	Pregnant women and perinates	(i) Societal (ii) Lifetime	(i) Treatment (ii) No treatment
Nicholson et al., 2005	Unites States	Screening for gestational diabetes mellitus	Pregnant women and children	To conduct a cost-effectiveness analysis to compare four screening strategies for universal screening of gestational diabetes mellitus	Pregnant women and perinates	(i) Societal (ii) Lifetime	(i) Four strategies for universal screening of gestational diabetes mellitus (ii) No screening strategies
Round et al., 2011	United Kingdom	Screening for gestational diabetes mellitus	Pregnant women and children	To estimate the cost-effectiveness of eight strategies	Pregnant women and perinates	(i) Healthcare system; societal (ii) Lifetime	(i) Eight strategies for screening

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				for screening for gestational diabetes			gestational diabetes mellitus (ii) No screening strategies
Labor and delivery complicated by vasa previa (n=1)							
Sinkey & Odibo, 2018	Unites States	Screening for vasa Previa	Pregnant women and children	To perform a decision and cost-effectiveness analysis comparing four screening strategies for the antenatal diagnosis of vasa previa in singleton pregnancies	Fetuses	(i) Healthcare system (ii) NS	(i) Ultrasound-indicated screening OR Screening only pregnancies conceived by in-vitro fertilization OR Universal screening (ii) No screening
Maternal care for known or suspected abnormality of pelvic organs (n=1)							
Xu et al., 2010	United States	Pelvic floor disorder	Pregnant women and children	To assess the cost-effectiveness of caesarean delivery on maternal request in comparison to trial of labor for prim gravid women without medical/obstetric indications with a	Pregnant women and neonates	(i) Societal (ii) Lifetime	(i) Caesarean delivery on maternal request (ii) Trial of labor

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				single childbirth over their lifetime, while explicitly accounting for the management of pelvic floor disorder			
Maternal care for suspected macrosomia (n=1)							
Wastlund et al., 2019	United Kingdom	Screening for macrosomia	Pregnant women and children	To identify the most cost-effective policy for detection and management of fetal macrosomia in late-stage pregnancy	Pregnant women and fetus	(i) Healthcare system (National heath service) (ii) 20 years	(i) Universal ultrasound scanning at 36 weeks of gestation (ii) Selective ultrasound scanning
Maternal infectious and parasitic diseases or fetus and newborn affected by maternal infectious and parasitic diseases (n=18)							
Sicuri et al., 2011	Spain	Screening of Chagas disease	Pregnant women and children	To conduct an economic evaluation of Chagas disease screening in pregnant women from Latin America and their newborns in the non-endemic area such as Spain	Pregnant women and neonates	(i) Societal (ii) NS	(i) Chagas disease screening (ii) No screening

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
Ong et al., 2015	Australia	Screening for Chlamydia	Pregnant women and children	To estimate the cost-effectiveness of screening all pregnant women aged 16–25 years for chlamydia compared with selective screening or no screening	Pregnant women	(i) Healthcare system (ii) One year	(i) Universal screening for Chlamydia (ii) Selective screening or no screening for Chlamydia
Albright et al., 2019	United States	Screening for Congenital cytomegalovirus	Pregnant women	To determine threshold cytomegalovirus infectious rates and treatment effectiveness to make universal prenatal Cytomegalovirus screening cost-effective	Perinates	(i) Healthcare system (ii) Lifetime	(i) Universal maternal serum screening (ii) Routine risk-based screening
Hersh et al., 2018	United States	Screening for Congenital syphilis	Pregnant women and children	To estimate the cost-effectiveness of screening for congenital syphilis for all women during the first and third	Fetuses	(i) Societal (ii) NS	(i) Screening for syphilis once at the first prenatal visit (ii) Screening for syphilis twice, once at the first prenatal visit and again at the

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				trimesters compared			beginning of the third trimester
Schackman et al., 2004	United States	Perinatal transmission of hepatitis C virus	Pregnant women and children	To determine the net health consequences, costs, and cost-effectiveness of elective caesarean delivery to prevent perinatal transmission of hepatitis C virus in human immunodeficiency virus (HIV) / hepatitis C virus (HCV) co-infected women with suppressed HIV RNA but detectable HCV RNA	Fetuses	(i) Societal (ii) Lifetime	(i) Elective caesarean delivery for all co-infected women with suppressed HIV RNA but detectable HCV RNA (ii) Elective caesarean delivery only when indicated based on fetal status
Little et al., 2005	United States	Herpes simplex virus	Pregnant women and children	To compare cost-effectiveness of acyclovir prophylaxis versus no acyclovir for women with a	Neonates	(i) NS (ii) Lifetime	(i) Acyclovir prophylaxis (ii) No Acyclovir prophylaxis

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				history of diagnosed genital herpes simplex virus infection but without recurrence in pregnancy			
Kuznik et al., 2012	Uganda	Human immunodeficiency virus (HIV) transmission during pregnancy	Pregnant women and children	To estimate the cost-effectiveness of combination antiretroviral therapy	Neonates	(i) Healthcare system (ii) 18 months	(i) Combination of antiretroviral therapy (ii) Standard care
Mrus et al., 2000	United States	HIV transmission during pregnancy	Pregnant women and children	To determine the net health consequences, costs, and cost-effectiveness of alternative delivery strategies for HIV-infected pregnant women with detectable HIV RNA	Neonates	(i) Societal (ii) Lifetime	(i) Elective caesarean section (i) Vaginal delivery
Mrus et al., 2004	United States	HIV transmission during pregnancy	Pregnant women and children	To evaluate the cost-effectiveness of rapid HIV testing followed by treatment with	Neonates	(i) Societal (ii) Lifetime	(i) Rapid HIV testing and administering zidovudine prophylaxis for

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				zidovudine, nevirapine, or combination therapy for pregnant women			women testing positive (ii) Not testing for HIV
VanDeusen et al., 2015	Ghana	HIV transmission during pregnancy	Pregnant women and children	To evaluate the cost effectiveness of Option B+ and Option B	Neonates	(i) NS (ii) Lifetime	(i) Option B+ (ii) Option B
Choi et al., 2017	Sub-Saharan Africa	Malaria	HIV-infected pregnant women and children	To assess the effectiveness and cost-effectiveness of daily cotrimoxazole relative to intermittent preventive treatment with sulfadoxine-pyrimethamine among HIV-infected pregnant women	Pregnant women	(i) Societal (ii) Lifetime	(i) Daily cotrimoxazole (ii) Sulfadoxine pyrimethamine
Sicuri et al., 2010	Mozambique	Malaria	Pregnant women and children	To conduct an economic evaluation of malaria preventive	Pregnant women and neonates	(i) NS (ii) Lifetime	(i) Sulphadoxine-pyrimethamine (ii) Standard treatment

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				strategies in pregnancy			
Orenstein et al., 2017	Mali	Maternal influenza immunization	Pregnant women and children	To estimate cost-effectiveness of maternal influenza immunization	Pregnant women and neonates	(i) Societal (ii) Lifetime	(i) Maternal influenza immunization (ii) No immunization
Xu et al., 2016	United States	Maternal seasonal influenza vaccination	Pregnant women and children	To evaluate the cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women	Pregnant women, neonates, and infants	(i) Societal (ii) NS	(i) Seasonal influenza vaccination (ii) No vaccination
Beigi et al., 2009	United States	Pandemic and seasonal influenza	Pregnant women and children	To assess the cost-effectiveness of universal maternal influenza vaccination using both a single and two-dose approach during seasonal and pandemic influenza outbreaks	Pregnant women, neonates, and infants	(i) Healthcare system; societal (ii) NS	(i) Vaccinating all pregnant women (ii) Not vaccinating all pregnant women

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
Lee et al., 2009	United States	Pandemic and seasonal Influenza	Pregnant women and children	To estimate the economic value of administering antiviral medications to pregnant women who have come in contact with an infectious individual with influenza	Pregnant women	(i) Healthcare system; societal (ii) NS	(i) Antiviral medications (ii) No antiviral medications
Hoshi et al., 2018	Japan	Pertussis	Pregnant women and children	To evaluate the cost-effectiveness of conducting antepartum maternal vaccination strategy	Neonates and infants	(i) Societal (ii) Four years	(i) Antepartum maternal vaccination (ii) No antepartum maternal vaccination
van Hoek et al., 2016	United Kingdom	Pertussis	Pregnant women and children	To investigate the cost-effectiveness of introducing maternal vaccination programme into the national immunisation schedule, offering a dose to women	Infants	(i) Healthcare system (ii) Lifetime	(i) Maternal vaccination (ii) No maternal vaccination

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				in every pregnancy			
Maternal and neonatal death (n=3)							
Jo et al., 2019	Bangladesh	Promoting care seeking of maternal and newborn health services	Pregnant women and children	To conduct the cost effectiveness analysis of mCARE strategies for promoting care seeking of maternal and newborn health services	Pregnant women and neonates	(i) NS (ii) Lifetime	(i)) Comprehensive mCARE package (ii)) Basic mCARE package
Prinja et al., 2018	India	Reducing maternal and newborn mortality	Pregnant women and children	To assess the cost effectiveness of mHealth intervention	Pregnant women and neonates	(i) Societal (ii) Nine years	(i) mHealth intervention (ii) No mHealth intervention
Goodman et al., 2017	Ghana	Reducing maternal and newborn mortality	Pregnant women and children	To evaluate the cost-effectiveness of a quality improvement intervention aimed at reducing maternal and fetal mortality	Pregnant women and fetuses	(i) NS (ii) Five years	(i) Health service quality improvement intervention (ii) No health service quality improvement intervention
Postpartum hemorrhage (n=1)							
Lubinga et al., 2015	Uganda	Postpartum hemorrhage	Pregnant women and children	To estimate the cost effectiveness of prenatal	Pregnant women	(i) Healthcare system (ii) Lifetime	(i) Prenatal misoprostol distribution

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				misoprostol distribution			(ii) No misoprostol distribution
Fetus or newborn affected by maternal use of tobacco (n=1)							
Jones et al., 2019	United Kingdom	Tobacco smoking during pregnancy	Pregnant women and children	To estimate the lifetime cost effectiveness of smoking cessation intervention	Pregnant women and perinates	(i) National Health Service (NHS); personal social services (PSS) (ii) Lifetime	(i) Smoking cessation intervention (ii) No intervention
Other disease(s) (n=3)							
Culligan et al., 2005	United States	Incontinence and brachial plexus injuries associated with macrosomia	Pregnant women and children	To determine the cost-effectiveness of a policy of elective C-section for macrocosmic infants to prevent maternal anal incontinence, urinary incontinence, and newborn brachial plexus injuries	Pregnant women and neonates	(i) NS (ii) Lifetime	(i) Spontaneous labor followed by either vaginal delivery or C-section (ii) Ultrasound a 39-week gestation followed by elective C-section for those women with estimated fetal weights of 4500g
Adam et al., 2005	Countries in sub-Saharan Africa and Southeast Asia	Various diseases and conditions	Pregnant women and children	To determine the costs and benefits of interventions for maternal and newborn health to assess the	Pregnant women and children	(i) NS (ii) Lifetime	(i) Maternal and newborn health services (ii) Standard care

Author, Year of publication	Country of population	Disease/ Condition	Participants	Aim/Objective	Intervention/ Treatment targeted toward	(i) Perspective (ii) Time Horizon	(i) Intervention (ii) Comparator(s)
				appropriateness of current strategies and guide future plans to attain the millennium development goals			
Babigumira et al., 2012	Uganda	Unintended pregnancies	Pregnant women and children	To estimate the potential cost-effectiveness of achieving universal access to modern contraceptives	Sexually active female	(i) Healthcare system (ii) Lifetime	(i) Universal access to modern contraceptives (ii) Traditional contraceptives

NS: not stated; fetus: an unborn offspring, from the embryo stage until birth; neonates: newborns until the first month of age; perinates: antenatal period up to seven days; infants: one month to one year of age

Appendix F Summary of the Quality of Pediatric Cost-utility Analyses

Reference	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Total score
Blicke et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Chodick et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	84
Coyle et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Hasen Edwards et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	91
Jit & Edmunds, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Melliez et al., 2008	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	57
Miline et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Newall et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Shim & Galvani, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	84
Tilson et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	87
Tu et al., 2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	68
Christensen et al., 2014	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	74

Tu et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Prosser et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	87
Blicke et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Chatterton et al., 2019	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	71
Creswell et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	87
Schawo et al., 2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	74
Tubeuf et al., 2019	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	74
Ulfsdotter et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	84
de Kinderen et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	87
O' Brien et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Prosser et al., 2004	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	70
Partridge et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	87

Notes: Sixteen criteria of the Quality of Health Economic Studies (QHES) instrument: Item 1. Was the study objective presented in a clear, specific, and measurable manner? (7 points); Item 2. Were the perspective of the analysis (societal, third party payer, etc.) and reasons for its selection stated? (4 points); Item 3. Were variable estimates used in the analysis from the best available source (i.e., randomized controlled trial—best, expert opinion—worst)? (8 points); Item 4. If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study? (1 point); Item 5. Was uncertainty handled by: (1) statistical analysis to address random events; (2) sensitivity analysis to cover a range of assumptions? (9 points); Item 6. Was incremental analysis performed between alternatives for resources and costs? (6 points); Item 7. Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 points); Item 8. Did the analytical horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3%–5%) and justification given for the discount rate? (7 points); Item 9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 points); Item 10. Were the primary outcome measure(s) for the economic evaluation clearly stated, and were the major short-term, long-term, and negative outcomes included? (6 points); Item 11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 points); Item 12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 points); Item 13. Were the choice of economic model, main assumptions and limitations of the study stated and justified? (7 points); Item 14. Did the author(s) explicitly discuss the direction and magnitude of potential biases? (6 points); Item 15. Were the conclusions/recommendations of the study justified and based on the study results? (8 points); Item 16. Was there a statement disclosing the source of funding for the study? (3 points). Y: Study met the criterion; N: All or part of the criterion was not met.

Appendix G Summary of the Quality of Maternal-perinatal Cost-utility Analyses

Reference	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Total score
Bak et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	91
Mistry et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Clennon et al., 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	75
Kastenberg et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Chung et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Gilbert et al., 2013a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	86
Gilbert et al., 2013b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Kaimal et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Tan et al., 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	71
Wymer et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Chen et al., 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	79
Danyliv et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Farrar et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Ohno et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94

Nicholson et al., 2005	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	71
Round et al., 2011	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	88
Sinkey & Odibi, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	71
Xu et al., 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	86
Wastlund et al., 2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	72
Sicuri et al., 2011	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	60
Ong et al., 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	72
Albright et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	91
Hersh et al., 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	69
Schackman et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Little et al., 2005	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	75
Kuznike et al., 2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	71
Mrus et al., 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	91
Mrus et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
VanDesusen et al., 2015	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	76
Choi et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94

Sicuri et al., 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	90
Orenstein et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	79
Xu et al., 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	68
Beigi et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	77
Lee et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	80
Hoshi et al., 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	71
Van Hoek et al., 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	71
Jo et al., 2019	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	73
Prinja et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Goodman et al., 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	90
Lubigna et al., 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	78
Jones et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94
Culligan et al., 2005	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	67
Adam et al., 2005	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	66
Babigumira et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	94

Notes: Sixteen criteria of the Quality of Health Economic Studies (QHES) instrument: Item 1. Was the study objective presented in a clear, specific, and measurable manner? (7 points); Item 2. Were the perspective of the analysis (societal, third party payer, etc.) and reasons for its selection stated? (4 points); Item 3. Were variable estimates used in the analysis from the best available source (i.e., randomized controlled trial—best, expert opinion—worst)? (8 points); Item 4. If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study? (1 point); Item 5. Was uncertainty handled by: (1) statistical analysis to address random events; (2) sensitivity analysis to cover a range of assumptions? (9 points); Item 6. Was incremental analysis performed between alternatives for resources and costs? (6 points); Item 7. Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 points); Item 8. Did the analytical horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3%–5%) and justification given for the discount rate? (7 points); Item 9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 points); Item 10. Were the primary outcome measure(s) for the economic evaluation clearly stated, and were the major short-term, long-term, and negative outcomes included? (6 points); Item 11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 points); Item 12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 points); Item 13. Were the choice of economic model, main assumptions and limitations of the study stated and justified? (7 points); Item 14. Did the author(s) explicitly discuss the direction and magnitude of potential biases? (6 points); Item 15. Were the conclusions/recommendations of the study justified and based on the study results? (8 points); Item 16. Was there a statement disclosing the source of funding for the study? (3 points). Y: Study met the criterion; N: All or part of the criterion was not met.

Appendix H Methods for Inclusion of Family Health Spillover Effects in Pediatric Cost-utility Analyses

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
Certain infectious and parasitic diseases (n=15)							
Bilcke et al., 2009	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D	HUI-2	0.002 QALY lost for the caregiver	• Statistical model (A deterministic compartmental static model)	• The mean total QALY losses for caregivers were estimated separately, and then the total QALY losses for caregivers and children were summed • A combined and separate total QALY gains or losses for caregivers and children due to the treatment reported
Chodick et al., 2009	QALY loss of the caregiver due to a child's illness or disability (s)	Two caregivers	EQ-5D	HUI-2	0.00184 QALY lost for each caregiver for each episode of rotavirus gastroenteritis	• Decision model includes health states for children (Markov model)	• The mean total QALY losses for caregivers and children were estimated separately, and then the mean total QALY losses for caregivers and children were summed • A combined mean total QALY gains or losses for caregivers and children due to the treatment reported

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
Coyle et al., 2012	Health utility of caregiver(s)	One caregiver	EQ-5D	HUI-2	0.967= Healthy caregiver 0.91=Caregiver of child with rotavirus	• Decision model includes health states for children	• Caregiver utility decrements or disutilities were subtracted from the child utilities only in the sensitivity analysis.
Hansen Edwards et al., 2017	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D-5L	HUI-2 with addition of the EQ-5D visual analogue scale	0.0082 QALY lost= Caregivers of inpatients 0.0046 QALY lost = Caregivers of outpatients 0.00145 QALY lost= Caregivers of home/ primary care patients	• Statistical model (A dynamic transmission model)	• Total QALY losses of caregivers and children were summed only in the sensitivity analysis
Jit and Edmunds, 2007	QALY loss of the caregiver due to a child's illness or disability (s)	Two caregivers	EQ-5D	HUI-2	0.00184 QALY lost for each caregiver per each episode of rotavirus gastroenteritis	• Statistical model (A cohort model)	• The mean total QALY losses for caregivers and children were estimated separately, and then the mean total QALY losses for caregivers and children were summed • A combined mean total QALY gains or losses for

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
							caregivers and children due to the treatment reported
Melliez et al., 2008	Health utility of caregiver(s)-child dyad	One caregiver	NA	NA	0.884= Child+ one carer in case of mild rotavirus diarrhoea 0.816= Child+ one carer in case of severe diarrhoea	• Decision model includes health states children	• Utilities estimated for caregiver and child-dyad • A combined mean total QALY gains or losses due to the treatment for caregivers and children was calculated and reported
Milne et al., 2009	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver (Two caregivers in sensitivity analysis)	EQ-5D	HUI-2	0.00184 QALY lost for each caregiver per each episode of rotavirus gastroenteritis	• Statistical model (A static equilibrium model)	• The mean total QALY losses for caregivers and children were estimated separately, and then the mean total QALY losses for caregivers and children were summed • A combined mean total QALY gains or losses for caregivers and children due to the treatment reported
Newall et al., 2007	QALY loss of the caregiver due to a child's	One caregiver (Two	EQ-5D	HUI-2	0.002 QALY lost for caregiver per hospitalisation/em	• Decision model includes health states	• The mean total QALY losses for caregivers were estimated separately, and

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
	illness or disability (s)	caregivers in sensitivity analysis)			ergency department visits/general practitioner visits for rotavirus	for children (Markov model)	then the total QALY losses for caregivers and children were summed • A combined and separate total QALY gains or losses for caregivers and children due to the treatment reported
Shim & Galvani, 2009	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D	HUI-2	0.002 QALY lost for a caregiver per hospitalization, emergency visit or general practitioner visits for children with rotavirus infections	• Statistical model (A dynamic transmission model)	• The mean total QALY losses for caregivers were estimated separately, and then the total QALY losses for caregivers and children were summed • A combined and separate total QALY gains or losses for caregivers and children due to the treatment reported.
Tilson et al., 2011	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D	HUI-2	NS	• Statistical model (A cohort model)	• Total QALY losses for caregivers and children were summed only in scenario analysis

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
Tu et al., 2012	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D	Derived from various studies that have used various preference-based health HRQoL instruments	0.00184 QALY lost for the caregiver per each episode of rotavirus gastroenteritis	• Decision model includes health states for children	• Total QALY losses of caregivers and children were summed only in sensitivity analysis
Christensen et al., 2014	QALY lost for family and network members due to a child's illness or disability(s)	The family and network members	NA	EQ-5D-Y	48% of QALY lost by children for family and network members An additional of 9% of the QALY lost by the death of the person with meningococcal disease for bereaved family and network members	• Statistical model (A dynamic transmission model)	• Total QALY gains or losses for family and network members and children were summed in sensitivity analysis
Tu et al., 2014	Disutility of a child's illness or disability on	One caregiver	EQ-5D	Derived from various studies that have used various	0.10= Disutility for caregiver of children experiencing	• Decision model includes health states for children	• Caregiver utility decrements or disutilities were subtracted from the

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
	the caregiver(s)			preference-based health HRQoL instruments	major congenital abnormalities		child utilities in sensitivity analysis
Prosser et al., 2011	QALY lost of caregiver(s) child dyad	One parent	Time-trade-off	Time-trade-off	Various QALY lost of caregiver(s)-child dyad for various pneumococcal diseases	• Decision model includes health states for children	• Total QALY losses for caregiver-child dyad were estimated, and then the total QALY losses for caregiver-child dyad were deducted from QALYs for each temporary health state. • A combined mean total QALY gains or losses for caregivers and children reported.
Bilcke et al., 2013	QALY loss of the caregiver due to a child's illness or disability (s)	One caregiver	EQ-5D	Derived from studies that have used various preference-based health HRQoL instruments	1.8 QALY lost for the caregiver per 1000 cases of rotavirus	• Statistical model (A dynamic model)	• Total QALY losses of caregivers and children were summed only in sensitivity analysis
Diseases of the blood or blood-forming organs (n=1)							

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
NICE, HST7, 2018	Family QALY lost due to patient premature death	Family	NS	NS	Family QALY loss 9% of child's QALY loss	• Decision model includes health states for children	• Total QALY gains or losses for caregivers applied to child QALY only in scenario analysis
Endocrine, nutritional, or metabolic diseases (n=2)							
NICE, HST2 2015	Disutility of a child's illness or disability on the caregiver(s)	One caregiver	NS	HUI-3	Disutility ranged from 0.00 to 0.14	• Decision model includes health states for caregivers and children	• Caregiver utility decrements or disutilites were subtracted from the child utilities • The mean total QALY losses or gains due to the treatment reported only for children
NICE HST8, 2018	Disutility of a child's illness or disability on the caregiver(s)	One caregiver	NS	EQ-5D	0.08= disutility	• Decision model includes health states for children	• Caregiver utility decrements or disutilities were subtracted from the child utilities only in scenario analysis
Mental, behavioral, or neurodevelopmental disorders (n=5)							
Chatterton et al., 2019	Health utility of caregiver(s)	One caregiver	AQOL-8D	CHU-9D	0.77= mean baseline health utility in intervention and	• Statistical mode (Under the curve method was applied to calculate total	• Utilities were estimated separately for caregivers and children, and then the mean total QALY losses or gains for caregivers and

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
					comparator groups 0.79= mean 12 months follow up health utility in intervention group, and 0.78= mean 12 months follow up health utility in comparator group	QALY losses or gains)	children due to the treatment were calculated separately • The mean total QALY losses or gains due the treatment reported separately for caregivers and children
Creswell et al., 2015	Health utility of caregiver(s)	Mother	EQ-5D	EQ-5D	0.833= mean baseline parental health utility in) child cognitive–behavioural therapy (CCBT)+ maternal cognitive–behavioural therapy (MCBT) group	• Statistical model (Under the curve method was applied to calculate total QALY losses or gains)	• Utilities were estimated separately for caregivers and children, and then the mean total QALY losses or gains for caregivers and children due to the treatment were calculated separately • The mean total QALY losses or gains due to the treatment reported separately for caregivers and children

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
					0.816= mean baseline health utility in CCBT group 0.824= mean 12-month follow up health utility in CCBT+MCBT group 0.814= mean 12-month follow health utility in CCBT group		
Schawo et al., 2015	Health utility of caregiver(s)	One caregiver	EQ-5D	EQ-5D	0.85= Health utility for a caregiver in optimal group 0.83= Health utility for caregiver in suboptimal group	• Decision model includes health states for children	• Utilities were estimated separately for caregivers and children, and utilities of caregivers and children were summed to estimate the total QALY losses or gains for caregivers and children • A combined total QALY gains or losses for

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
					0.83 = Health utility for caregiver in treatment stopped group		caregivers and children reported
Tubeuf et al., 2019	Health utility of caregiver(s)	One parent	HUI-2	EQ-5D-3L	Baseline TAU=0.70 FT=0.72 <u>6 months</u> Treatment as usual (TAU)=0.77 Family therapy FT=0.76 <u>12 months</u> TAU=0.78 FT=0.78	• Statistical model	• Utilities were estimated separately for caregivers and children, and the mean total QALY losses for caregivers and children due to the treatment were calculated separately and then, the mean total QALY losses due to the treatment for caregivers and children were summed • A combined and separate total mean QALY gains or losses due to the treatment for caregivers and children reported
Ulfsdotter et al.,2015	NA	One parent	QALY obtained through	EuroQol Group's VAS (EQ-VAS)	NA	• Statistical model	• Utilities were estimated separately for caregivers and children, and the mean

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
			mapping GHQ-12				total QALY losses for caregivers and children due to the treatment were calculated separately and then, the mean total QALY losses due to the treatment for caregivers and children were summed • A combined and separate total mean QALY gains or losses due to the treatment for caregivers and children reported
Diseases of the nervous system (n=2)							
de Kinderen et al., 2016	Health utility of caregiver(s)	NS	EQ-5D-Y	EQ-5D	0.29= Ketogenic diet 0.27= Care as usual	• Statistical model (under the curve method was applied to calculate total QALY losses or gains)	• Utilities were estimated separately for caregivers and children, and then the mean total QALY losses or gains for caregivers and children due to the treatment were calculated separately • The mean total QALY losses or gains due to the treatment reported

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
							separately for caregivers and children
NICE, HST3, 2016	Disutility of a child's illness or disability on the caregiver(s)	Company original submission: 1 carer. Company revised model: 3 carers. ERG analysis: 2 carers	EQ-5D	NS	0.11= Disutility for each caregiver	• Decision model includes health states for children	• Caregiver utility decrements or disutilites were subtracted from the child utilities • The mean total QALY losses or gains due to the treatment reported only for children
Diseases of the ear or mastoid process (n=2)							
O'Brien et al., 2009	QALY lost of caregiver(s)-child dyad	One parent	Time-trade-off	Time-trade-off	0.011= AOM 0.11=Tympanostomy-tube insertion 0.18=Pneumonia 0.59=Complicated pneumonia 0.21=Bacteremia 0.76= Meningitis	• Statistical model	• Total QALY losses for caregiver-child dyad were estimated, and then the total QALY losses or gains caregiver-child dyad were estimated. • A combined total QALY gains or losses for caregivers and children reported.

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
Prosser et al., 2004	QALY lost of caregiver(s)-child dyad	One parent	Time-trade-off	Time-trade-off	Various QALY lost of caregiver(s)-child dyad for various pneumococcal diseases	NA	• Total QALY losses for caregiver-child dyad were estimated, and then the total QALY losses or gains caregiver-child dyad were estimated. • A combined mean total QALY gains or losses for caregivers and children reported
Diseases of musculoskeletal system or connective tissue (n=1)							
NICE, TA373, 2015	Disutility of a child's illness or disability on the caregiver(s)	One caregiver	EQ-5D	NS	0.02 or 0.07= disutility when a child off treatment	• Decision model includes health states for children	• Caregiver utility decrements or disutilities were subtracted from the child utility only in scenario analysis
Certain conditions originating in the perinatal period(n=1)							
Partridge et al., 2015	Health utility of caregiver (s)	Mother	NS	HUI-2	1.00= Intact survival 0.90= Mild sequelae 0.80= Moderate impairment 0.75= Severe disability	• Two decision models health states for children • One comparing universal resuscitation with no resuscitation and the second comparing	• Utilities were estimated separately for caregivers and children, and the mean total QALY losses for caregivers and children due to the treatment were calculated separately and then, the mean total QALY

Author, Year of publication	Family health spillover outcome	Family health spillover effects measured in family members	Instrument used in family members	Instrument used in child	Magnitude of health spillover effect	Modeling approach	Integration of family health spillover effects
					0.90= Infant death	selective resuscitation with no resuscitation	losses due to the treatment for caregivers and children were summed • A combined and separate total mean QALY gains or losses due to the treatment for caregivers and children reported

NICE: National Institute for Health and Care Excellence; HST: highly specialized technologies; TA: technology appraisal; NHS: National Health Service; PSS: personal social services; NS: not stated; QALY: quality-adjusted life year; CHU-9D: Child Health Utility 9D; EQ-5D: EuroQol 5D; EQ-5D-3L: The 3-level version of EQ-5D; EQ-5D-Y: Child-friendly EQ-5D version; AQoL-8D, HUI-2; Health Utilities Index -Mark 2.

Appendix I Methods for Integration of Mother and Child Health Outcomes in Maternal-perinatal Cost-utility Analyses

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
Diseases of the circulatory system (n=3)							
Bak et al., 2020	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	1.0=no cerebral palsy 0.82=mild cerebral palsy 0.63=moderate cerebral palsy 0.21=severe cerebral palsy	0.87= mild cerebral palsy 0.76=moderate cerebral palsy 0.60= severe cerebral palsy 0.92= neonatal death/intrauterine fetal demise 0.92= termination of pregnancy	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Mistry et al., 2013	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	Various health utilities were used for no disability, mild congenital heart disease (CHD), moderate CHD, and severe disability.	Various health utilities were used for different health states during the pregnancy	• Decision model includes health states for pregnant women and children*	Utilities were estimated separately for pregnant women and children, and the mean total QALYs for pregnant women and children summed • A combined mean total QALY gains or

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							losses for pregnant women and children due the treatment reported
Clennon et al., 2021	Health utilities of pregnant women and children	Derived from the literature and authors' assumption	Derived from the literature and authors' assumption	Various health utilities were used for different health states for children	Various health utilities were used for different health states for pregnant women	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Diseases of appendix (n=1)							
Kastenberg et al., 2013	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.70= premature 0.80= cancer 0.56=premature and cancer	0.73= acute appendicitis	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							• A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Delivery (n=6)							
Chung et al., 2001	Health utilities of pregnant women and children	NS	QWB	1= no/mild or moderate morbidity 0=0.6 severe morbidity 0=death	1= perfect health 0.963= well after hysterectomy 0=death	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Gilbert et al., 2013a	Disutilities for pregnant women and children associated	Derived from the literature	Derived from the literature	0.44= Cerebral palsy 0.75= hypoxic ischemic encephalopathy (HIE)	0.45= Elective repeat caesarean delivery (ERCD)/indicated repeat 0.49= Uterine rupture	• Decision model includes health states for pregnant	• Disutilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
	with the disease				0.47= Failed trial of labor after a previous caesarean (TOLAC) 0.35= Successful TOLAC 0.19= Urinary stress incontinence	women and children	and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Gilbert et al., 2013b	Disutilities for pregnant women and children associated with the disease	Derived from the literature	Derived from the literature	0.44= Cerebral palsy 0.75=HE	0.45= ERCD/indicated repeat 0.49= uterine rupture 0.47= failed TOLAC 0.35= successful TOLAC 0.19= urinary stress incontinence	• Decision model includes health states for pregnant women and children	• Disutilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Kaimal et al., 2011	Health utilities of pregnant women and children	Derived from the literature	Derived from literature and authors' assumption	1= healthy neonates 0= intrauterine fetal demise	0.99= caesarean delivery 0.92= intrauterine fetal demise 1= vaginal delivery	• Decision model includes health states for pregnant	• Utilities were estimated separately for pregnant women and children, and the mean total QALY

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
						women and children	for pregnant women and children were summed • A combined total mean QALY gains or losses for pregnant women and children due to the treatment reported
Tan et al., 2010	Health utilities of pregnant women and children	Authors' assumption	Authors' assumption	1= well health after vaginal delivery 1=well after caesarean delivery 0.58= adverse outcome following emergency caesarean	0.86= well health after vaginal delivery 0.78= well after caesarean delivery 0.76= adverse outcome following emergency caesarean	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Wymer et al., 2014	Health utilities of pregnant	Derived from the literature	Derived from the literature	Various health utilities were used for difference states for neonate	Various health utilities were used for different health states during the pregnancy.	• Separate decision-analytic models of	• Utilities were estimated separately for pregnant women and children, and the

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
	women and children					pregnant women and neonates were constructed.	mean total QALY estimated separately for pregnant women and children • The mean total QALY gains or losses due to the treatment for pregnant women and children were reported separately
Diabetes mellitus (n=6)							
Chen et al., 2016	Health utilities of pregnant women and children	Derived from the literature and estimated from expert opinion	Derived from the literature and estimated from expert opinion	0.00= neonatal death 0.99= shoulder dystocia and transient brachial plexus injury 0.70= hyperbilirubinemia 0.70= hypoglycemia 0.50= NICU admissions	0.99= preeclampsia 0.80= maternal diabetes for overt diabetes mellitus (DM) only 1= normal vaginal delivery 0.99= elective lower segment caesarean section (LSCS) 0.95=emergency LSCS 0.80=macrosomia 0.92=neonatal death	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
Danyliv et al., 2016	QALY loss of pregnant women and children due to the disease	WHO-QOL-BREF questionnaire	Derived from the literature	0.04 to 0.96= QALY loss because of premature birth 0.6= QALY lost due to brachial plexus injury	0.92=QALY lost because of stillbirth 0.0042 to 0.9548= QALY lost because of premature birth	• Decision model includes health states for pregnant women and children	• The mean total QALY losses for mothers and children were estimated separately, and then the mean total QALY losses for mothers and children were summed • A combined mean total QALY gains or losses for mothers and children reported
Farrar et al., 2016	QALY loss of pregnant women and children due to the disease	Derived from the literature	Derived from the literature	0.179= QALY lost due to shoulder dystocia 0.179= QALY lost due to birth trauma 25= QALY lost due to neonatal death	24.8 = QALY lost due to maternal death 9.79= QALY lost due to hysterectomy 4.43= QALY lost due to hypoxic-ischaemic encephalopathy 2.77= QALY loos due to urinary incontinence	• Decision model includes health states for pregnant women and children	• The mean total QALY losses for mothers and children were estimated separately, and then the mean total QALY losses for mothers and children were summed • A combined mean total QALY gains or losses for mothers

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							and children reported
Ohno et al., 2011	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0= neonatal death 0.99= transient brachial plexus injury 0.6= transient brachial plexus moderate injury 0.45= transient brachial plexus severe injury	1= vaginal delivery 0.99= caesarean delivery 0= maternal death 0.92= neonatal death from maternal perspective	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Nicholson et al., 2005	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.7= moderate morbidity 0=severe morbidity and neonatal death	0.9= perfect health following hysterectomy 0= maternal death	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for mothers and children were summed • The mean total QALY gains or losses due to the

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							treatment for pregnant and children reported separately
Round et al., 2011	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	Various health utilities for different health states of children	Various health utilities for different health states of pregnant women	• Decision model included health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Labor and delivery complicated by vasa previa (n=1)							
Sinkey and Odibo, 2018	QALYs of pregnant-children dyad	Derived from the literature	Derived from the literature	**<u>Maternal–neonatal dyad QALY</u>** 17 QALY= No maternal morbidity, infant survives 16.9= Maternal morbidity, infant survives 15.3= No maternal morbidity, infant dies 15.2= Maternal morbidity, infant dies		• Decision model includes health states for pregnant women and children	• Total pregnant women-child dyad QALY estimated • A combined mean total QALY gains or losses for pregnant women and children due to the treatment

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							was calculated and reported
Maternal care for abnormality of pelvic organs (n=1)							
Xu et al., 2010	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	Various health utility and disutility	Various health utility and disutility	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Maternal care for excessive fetal growth (n=1)							
Wastlund et al., 2019	Health utilities of pregnant women and children	Derived from the literature	Authors' assumption	0.95= brachial plexus injury short-term 0.6= brachial plexus injury long-term 0.975= anoxia- short-term 0.63=severe anoxic brain damage	0.939= delivery vaginal 0.882= delivery-ELCS 0.935=delivery EMCS	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							• A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported.
Maternal infectious and parasitic diseases (n=18)							
Sicuri et al., 2011	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.9625=indeterminate phase 0.71705= cardio/digestive problems 0.769= average between mild cardio problems 0.6651=strong cardio problems	0.9625=indeterminate phase 0.71705= cardio/digestive problems 0.769= average between mild cardio problems 0.6651=strong cardio problems	• Two decision models • Pregnant women and newborn decision model include health states for pregnant women and children • Pregnant women decision model includes health states	• Utilities were estimated separately for the pregnant women and children, and the mean total for caregivers and children were estimated separately and then, the mean total QALY for caregivers and children were summed • A combined and separate mean total QALY gains or losses due to the treatment for caregivers and children reported

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
						for pregnant women	
Ong et al., 2015	Health utilities of pregnant women and children	Derived from the literature and authors' assumption	Authors' assumption	0.8= low birth weight baby 0.79= neonatal pneumonia 0.65= pelvic inflammatory disease 0.6= postpartum endo metritis 0.9= symptomatic chlamydia 0.97= neonatal conjunctivitis 0.95= test positive 1.0= no chlamydia	0.95= women who have tested positive for chlamydia	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Albright et al., 2019	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature and authors' assumption	0.48=severe disability 0= death	0.94= pregnancy termination 0.94=miscarriage or fetal loss 0.92= intrauterine fetal demise 0.92= neonatal death 0.5= delivery of a severely affected child from	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children estimated separately • The mean total QALY losses or gains due to the

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
					cytomegalovirus or cerebral palsy 1= delivery of a healthy child		treatment reported separately for pregnant women and children
Hersh et al., 2018	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.74= congenital syphilis	0.92= intrauterine fetal demise neonatal or infant death=0.76 congenital syphilis=0.88	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Schackman et al., 2004	Disutilities associated with the disease for and QALY of pregnant women and children	Derived from the literature	Derived from the literature	28.7= QALY for healthy infant 18.2= QALY infant that develops chronic hepatitis C virus (HCV) as an adult	7.6= QALY for HIV/HCV-co-infected mother surviving delivery 0.02= disutility of complication 0.02= disutility of caesarean section	• Decision model includes health states for pregnant women and children	• The mean total QALY or disutilities were estimated separately for pregnant women and children • The mean total QALY gains or losses due to the

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							treatment for pregnant women and children reported separately
Little et al., 2005	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.9= moderate disability of neonates 0.3= severe disability of neonates	0.99= caesarean delivery 0.81= having an impaired child 0.92= losing a child	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported
Kuznik et al., 2012	DALY averted for pregnant women and children	NA	NA	0.123= for each year lived with HIV infection 0.505= for the last year of life with AIDS	0.123= for each year lived with HIV infection 0.505= for the last year of life with AIDS	• Decision model includes health states for pregnant women and children	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							children were summed • A combined mean total DALY averted due to the treatment for pregnant women and children reported
Mrus et al., 2000	Disutilities associated with the disease for and QALY of pregnant women and children	Derived from the literature	Derived from the literature	29.6= QALYs for healthy infant 9.7= QALYs for infant infected with HIV	9.8= QALYs for mother if survives delivery 0.02= disutility of complication 0.02= disutility of caesarean section	• Decision model includes health states for pregnant women and children	• The mean total QALY or disutilities were estimated separately for pregnant women and children • The mean total QALY gain or losses due to the treatment for pregnant women and children reported separately
Mrus & Tsevat., 2004	QALY of pregnant women and children	Derived from the literature	Derived from the literature	9.7=QALYs for HIV-infected infant 29.7= QALYs for uninfected infant	7.6=QALYs for infected HIV-women 22.6= QALYs for uninfected women	• Decision model includes health states for pregnant women and children	• The mean total QALY for pregnant women and children estimated separately, and then the mean total QALY gains, or losses were summed

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							• A combined mean total QALY gains or losses for pregnant women and children reported
VanDeusen et al., 2015	QALY lost of pregnant women and children	NS	NS	0.82 times QALY healthy adult women= mothers with HIV	0.82 times QALY of healthy children =children with HIV	• Decision model includes health states for pregnant women and children	• The mean total QALY losses for mothers and children were estimated separately, and then the mean total QALY losses for mothers and children were summed • A combined mean total QALY gains or losses for mothers and children reported.
Choi et al., 2017	DALY averted for pregnant women and children	NA	NA	0.11= Low birth weight	0.21= malaria during pregnancy 0.006= maternal anaemia due to malaria	• Decision model includes health states for pregnant women and children	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							children were summed • A combined mean total DALY averted due to the treatment for pregnant women and children reported
Sicuri et al., 2010	DALY averted pregnant women and children	NA	NA	NS	NS	• Decision model includes health states for pregnant women and children	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total DALY averted due to the treatment for pregnant women and children reported
Orenstein et al., 2017	DALY averted pregnant	NA	NA	57.28= DALY lost for infant death or stillbirth	32.27= DALY lost for maternal death	• Decision model includes	• The mean total DALY averted for pregnant women and

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	women and children					health states for pregnant women and children	children were estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total DALY averted due to the treatment for pregnant women and children reported
Xu et al., 2016	Health utilities of pregnant women and children	Derived from the literature	Derived from the literature	0.95= hospitalized infant 0.99= outpatient infant	0.5=hospitalized mother 0.65=outpatient mother 0.99= minor adverse effects on mother 0.5= Guillain-Barre syndrome	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean QALY gains or losses for pregnant women and children due to the treatment reported

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
Beigi et al., 2009	QALY of pregnant women and children	Derived from the literature	Derived from the literature	Not clear	Not clear	• Decision model includes health states for pregnant women and children	• Not clear • A mean combined QALY gains or losses for mother and children reported
Lee et al., 2009	QALY of pregnant women and children and QALY loss of pregnant women and children due to the disease	Derived from the literature	Derived from the literature	Various QALY and QALY loss were used for different health states for children	Various QALY and QALY loss were used for different health states for pregnant women	• Decision model includes health states for pregnant women and children	• The mean total QALY and QALY losses for pregnant women and children were estimated separately and the mean total QALY for pregnant women and children were summed • A combined mean total QALY for pregnant women and children due to the treatment was reported.
Hoshi et al., 2018	Heath utilities of pregnant	Derived from the literature and estimated	Derived from the literature and estimated	0.58= hospitalised infant 0.29= mechanical ventilation infant	0.85= mild to moderate illness mother	• Decision model includes health states	• Utilities were estimated separately for pregnant women and children, and the

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
	women and children	from expert opinion	from expert opinion		0.82= hospitalised mother 0.81= mother with asthma	for pregnant women and children	mean total QALY for pregnant women and children were estimated separately • The mean total QALY gains or losses due to the treatment for pregnant women and children reported separately
van Hoek et al., 2016	QALY loss of pregnant women and children due to the disease and disutilities associated with the disease for children and pregnant women	Authors' assumption	Derived from the literature	65.1=QALY loss in case of death 0.1007=QALY loss in surviving infants	0.03645= mild disease 0.09724= laboratory confirmed disease	• Decision model includes health states for pregnant women and children	• The mean QALY loss and disutilties were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean QALY gains or losses for pregnant women and children due to the treatment reported

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
Maternal and neonatal death (n=3)							
Jo et al., 2019	DALY averted pregnant women and children	NA	NA	NS	NS	• Statistical model	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total DALYs averted due to the treatment for pregnant women and children reported
Prinja et al., 2018	DALY averted for pregnant women and children	NA	NA	NS	NS	• Decision model includes health states for pregnant women and children	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and children were summed

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							• A combined and separate mean total DALY averted due to the treatment for pregnant women and children reported
Goodman et al., 2017	DALY averted for pregnant women and children	NA	NA	NS	NS	• Statistical model	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total DALY averted due to the treatment for pregnant women and children reported
Postpartum hemorrhage (n=1)							
Lubinga et al., 2015	DALY averted for pregnant	NA	NA	NS	NS	• Decision model includes health states	• The mean total DALY averted for pregnant women and children were

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	women and children					for pregnant women and children	estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total DALY averted due to the treatment for pregnant women and children reported
Tobacco use disorder (n=1)							
Jones et al., 2019	Health utilities for children and disutilities associated with disease for pregnant women	Derived from the literature	Derived from the literature	1= perfect health 0.9= asthma	0.1=disutility for women who experienced a fetal loss 0.01= an additional disutility for ectopic pregnancy 0.73= smoking related morbidities 0.73= coronary heart disease 0.72= chronic obstructive pulmonary disease	• Decision model includes health states for pregnant women and children	• Utilities were estimated separately for pregnant women and children, and the mean total QALY for pregnant women and children were summed • A combined mean total QALY gains or losses for pregnant women and children due to the treatment reported

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
					0.67= lung cancer 0.72=stroke		
Other diseases and conditions (n=3)							
Culligan et al., 2005	Health utilities of pregnant women-child dyad	Expert panel assumptions	Expert panel assumptions	Various health utilities were used for a pregnant women-child dyad		• Decision model includes health states for pregnant women and children	• Utilities were estimated for pregnant women-child dyad • A combined mean total QALY gains or losses due to treatment for pregnant women and children was calculated and reported.
Adam et al., 2005	DALY averted for pregnant women and children	NA	NA	NS	NS	• NS	• The mean total DALYs averted for pregnant women and children were estimated separately, and then mean total DALY averted for pregnant women and children were summed • A combined and separate mean total

Author, Year of publication	Health outcomes of children and pregnant women	Instrument used in pregnant women	Instrument used in children	Health utilities or disability weights or QALY or DALY of children	Heath utilities or disability weights or QALY or DALY of mothers/ pregnant women	Modeling approach	Integration of health outcomes of children and pregnant women/mothers
							DALY averted due to the treatment for pregnant women and children reported
Babigumira et al., 2012	DALY averted for pregnant women and children	NA	NA	NS	NS	• Decision model includes health states for pregnant women and children	• The mean total DALY averted for pregnant women and children were estimated separately, and then mean total DALY averted due to the treatment for pregnant women and children were summed • A combined and separate mean total DALY averted due the treatment for pregnant women and children reported

QALY: quality-adjusted life year; DALY: disability-adjusted life year; NS: not stated; NA: not applicable

Appendix J Research Ethics Board (REB) Study Approval Letter

Wendy Ungar
Child Health Evaluative Sciences

REB number: 1000066220

Study Title: The impacts of paediatric neuroinflammatory disorders on the parent health-related quality of life and associated productivity loss

Date of Approval: 2020-02-01
Expiry Date: 2021-02-01

Thank you for the application submitted on **2019-10-23.** The above referenced study was reviewed through a delegated process (not by Full Board review). Any concerns arising from this review have been documented and resolved.

The REB voted to approve this study, and your participation as Principal Investigator, as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004.

The Hospital for Sick Children Research Ethics Board hereby issues approval for the above named study. This approval is effective from **2020-02-01** to **2021-02-01.** Continuation beyond that date will require further review of REB approval.

The following documents have been reviewed and are approved:

1. **Protocol version dated January 13, 2020 [ND_Protocol_13JAN2020_clean .docx (1.0)]**
2. **Parent Consent Form version dated January 13, 2020 [ND_ParentGuardain ConsentForm_13JAN2020_clean .docx (1.0)]**
3. **Participant Consent Form version dated January 13, 2020 [ND_Participant ConsentForm_13JAN2020_clean.docx (1.0)]**
4. **Assent Form version dated January 13, 2020 [ND_Assent Form_13JAN2020_clean .docx (1.0)]**
5. **Demographic Questionnaire version dated January 13, 2029 [ND_Demographic questionnaire_13JAN2020_clean.docx (1.0)]**
6. **Carer QoL Parent Questionnaire version dated January 13, 2020 [ND_CarerQoLParent_13JAN2020_clean .docx (1.0)]**
7. **Health Utilities Index Form for Parent Health version dated September 30, 2019 ND_HUIFor Parent Health_30SEP2019.doc (1.0)]**
8. **Health Utilities Index Form for Child Health version dated September 30, 2019 [ND_HUIForChildHeatlh_30SEP2019.doc (1.0)]**

9. Resource Use Questionnaire version dated September 30, 2019 [ND_RUQ_30SEP2019.docx (1.0)]

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB.

Kathy Boutis REB Vice-Chair

555 University Avenue, Toronto,
ON M5G 1X8 Tel: (416) 813-8279
Fax: (416) 813-6515

The SickKids REB operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing. The REB has reviewed and approved the clinical trial protocol and informed consent form for the trial. All investigational drug trials at SickKids are conducted by qualified investigators.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

Appendix K Demographic Questionnaire

Demographic Information: Child and Parent(s)- Impacts of paediatric neuroinflammatory disorders on parents

Participant ID: _____

Date: _____

In this section, please answer questions about your child

---

1. Your child's age (in years), if applicable _____

2. Your child's sex, as it was assigned on their birth certificate:
   - Female
   - Male
   - Not specified/Prefer not to say

3. With respect to your child's gender, does your child identify as
   - Girl
   - Boy
   - Transgender
   - Do not identify as a girl, boy or transgender
   - Not specified/Prefer not to answer
   - Not applicable

In this section, please answer questions about the first parent

Information about Parent #1

---

4. Which best describes your relationship with your child. I am the…….
   - Mother
   - Father
   - Stepmother
   - Stepfather
   - Legal guardian
   - Foster parent
   - Other (please specify) ……

5. Your age (in years) _____

6. Your sex, as it was assigned on your birth certificate:
    - Male
    - Female
    - Not specified/Prefer not to say

7. Your gender; you identify yourself as
    - Man
    - Woman
    - Transgender
    - Do not identify as woman, man or transgender
    - Not specified/Prefer not to answer
    - Other

If other, please specify _____

8. Your marital status
    - Never married
    - Married
    - Domestic partnership (you are unmarried but have a relationship with your partner, and you live together)
    - Divorced
    - Separated
    - Widowed
    - Not specified/ Prefer not to answer
    - Other

If other, please specify _____

9. Which best describes your household? In your house, there are one or more child(ren) and……
    - Both parents (mother and father)
    - Parent and stepparent
    - Single parent
    - Foster parent(s)
    - Adoptive parent(s)
    - Legal guardian(s)
    - Not specify/Prefer not to answer
    - Other

If other, please specify _____

10. How many dependent children live in your household?
    - 1
    - 2
    - 3
    - 4
    - 5
    - 6
    - 7 or more

11. Total number of adults living in your household
    - 1
    - 2
    - 3
    - 4
    - 5
    - 6
    - 7 or more

12. Which population group do you most identify with?
    - White
    - Black (e.g. African, Haitian, Jamaican, Somali, etc.)
    - Chinese
    - South Asian (e.g. East Indian, Pakistani, Punjabi, Sri Lankan, etc.)
    - Native/Aboriginal (North American Indian, Métis, Inuit/Eskimo, etc.)
    - Arab/West Asian (e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan, etc.)
    - Filipino
    - Southeast Asian (e.g. Cambodian, Indonesian,
    - Laotian, Vietnamese, etc.)
    - Latin American
    - Japanese
    - Korean
    - Not specify/Prefer not to answer
    - Other

If other, please specify _____

13. What is the highest level of schooling/education that you have successfully completed?
    - 8th grade or less
    - 9th - 12th grade, no diploma
    - High school graduate or General Equivalency Development (GED) completed

- Some college credit but no degree
- Occupational/technical/vocational program
- Associate degree (e.g., AA, AS)
- Bachelor's degree (e.g., BA, AB, BS)
- Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)
- Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)
- Not specified / Prefer not to answer
- Unknown
- Other

If other, please specify _____

14. Current employment status
    (Please check all that apply)
    - Working now-Full-Time
    - Working now - Part-Time
    - Only temporarily laid off, on sick leave, or on maternity leave
    - Looking for work and/or unemployed
    - Retired
    - Disabled, permanently or temporarily
    - Stay-at-home parent/Caregiver (unpaid)
    - Volunteer
    - Student
    - Not specified / Prefer not to answer
    - Other

If other, please specify _____

15. What is your combined, gross family income? Gross income is total income before taxes or reductions
    - Under $15,000
    - $15,000 to $24,999
    - $25,000 to $34,999
    - $35,000 to $49,999
    - $50,000 to $74,999
    - $75,000 to $99,999
    - $100,000 to $199,999
    - $200,000 and over
    - Not specified / Prefer not to say
    - Unknown

16. Are there any special circumstances in your family that (you feel) has affected your ability to care for your child (Please check all that apply)- **(Note: Please preface parents to not reveal the names of other family members diagnosed with medical conditions)**
    - ○ Another member (s) of your family has been diagnosed with a medical condition

Please specify _____

Please specify your relationship to the family member

    - ○ Your personal health, including mental health

Please specify _____

    - ○ Death in the family
    - ○ Immigration to Canada
    - ○ Not applicable
    - ○ Prefer not to say
    - ○ Other

If other, please specify _____

Appendix L Health Utilities Index (HUI) For Parents

Impacts of paediatric neuroinflammatory disorders on parents
Health Utilities Index (HUI) –Parent of Participant

The next set of questions asks about various aspects of your health. When answering these questions, we would like you to think about your health and your ability to do things on a day-to-day basis, during the past week. To define the "past week period", please think about what the date was 7 days ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past week.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

---

1. VISION

1. During the past week, have you been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?
   - ○ Yes → **Go to 4**
   - ○ No
   - ○ Don't know
   - ○ Refused

2. Have you been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?
   - ○ Yes → **Go to 4**
   - ○ No
   - ○ Don't know/Didn't wear glasses or contact lenses
   - ○ Refused

3. During the past week, have you been able to see at all?
   - ○ Yes
   - ○ No → **Go to 6**
   - ○ Don't know
   - ○ Refused

4. During the past week, have you been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?
   - ○ Yes → **Go to 6**
   - ○ No
   - ○ Don't know
   - ○ Refused

5. Have you been able to see well enough to recognize a friend on the other side of the street *with* glasses or contact lenses?

- ○ Yes
- ○ No
- ○ Don't know/Didn't wear glasses or contact lenses
- ○ Refused

2. HEARING

6. During the past week, have you been able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

7. Have you been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?

- ○ Yes → **Go to 9**
- ○ No
- ○ Don't know/Didn't wear a hearing aid
- ○ Refused

8. During the past week, have you been able to hear at all?

- ○ Yes
- ○ No → **Go to 11**
- ○ Don't know
- ○ Refused

9. During the past week, have you been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

10. Have you been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?

- ○ Yes
- ○ No
- ○ Don't know/Didn't wear a hearing aid
- ○ Refused

3. SPEECH

11. During the past week, have you been able to be understood *completely* when speaking your own language with people who do not know you?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

12. Have you been able to be understood *partially* when speaking with people who do not know you?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

13. During the past week, have you been able to be understood *completely* when speaking with people who know you well?
- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

14. Have you been able to be understood *partially* when speaking with people who know you well?
- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

15. During the past week, have you been able to speak at all?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

4. GETTING AROUND

16. During the past week, have you been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

17. Have you been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

18. Have you been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

19. During the past week, have you been able to walk at all?
- ○ Yes
- ○ No → **Go to 22**
- ○ Don't know
- ○ Refused

20. Have you needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

21. Have you needed the help of another person to walk?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

22. Have you needed a wheelchair to get around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

23. Have you needed the help of another person to get around in the wheelchair?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

5. HANDS AND FINGERS

24. During the past week, have you had the *full use* of both hands and ten fingers?
- ○ Yes → **Go to 28**
- ○ No
- ○ Don't know
- ○ Refused

25. Have you needed the help of another person because of limitations in the use of your hands or fingers?
- ○ Yes
- ○ No → **Go to 27**
- ○ Don't know
- ○ Refused

26. Have you needed the help of another person with some tasks, most tasks, or all tasks?
- ○ Some tasks
- ○ Most tasks
- ○ All tasks
- ○ Don't know
- ○ Refused

27. Have you needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of your hands or fingers?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

6. SELF-CARE

28. During the past week, have you been able to eat, bathe, dress and use the toilet without difficulty?
- ○ Yes → **Go to 31**
- ○ No
- ○ Don't know
- ○ Refused

29. Have you needed the help of another person to eat, bathe, dress or use the toilet?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

30. Have you needed special equipment or tools to eat, bathe, dress or use the toilet?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

7. FEELINGS

31. During the past week, have you been feeling happy or unhappy?

- ○ Happy
- ○ Unhappy → **Go to 33**
- ○ Don't know
- ○ Refused

32. Would you describe yourself as having felt:
(a) happy and interested in life, or
(b) somewhat happy?

- ○ a → **Go to 34**
- ○ b → **Go to 34**
- ○ Don't know
- ○ Refused

33. Would you describe yourself as having felt:
(a) somewhat unhappy
(b) very unhappy
(c) so unhappy that life was not worthwhile

- ○ a
- ○ b
- ○ c
- ○ Don't know
- ○ Refused

34. During the past week, did you ever feel fretful, angry, irritable, anxious or depressed?

- ○ Yes
- ○ No → **Go to 37**
- ○ Don't know
- ○ Refused

35. How often did you feel fretful, angry, irritable, anxious or depressed: rarely, occasionally, often, or almost always?

- ○ Rarely
- ○ Occasionally
- ○ Often
- ○ Almost always
- ○ Don't know
- ○ Refused

36. During the past week did you feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

8. MEMORY

37. How would you describe your ability to remember things, during the past week:
(a) able to remember most things
(b) somewhat forgetful
(c) very forgetful
(d) unable to remember anything at all?

- ○ *a*
- ○ *b*
- ○ *c*
- ○ *d*
- ○ *Don't know*
- ○ *Refused*

9. THINKING

38.	How would you describe your ability to think and solve day to day problems, during the past week: (a) able to think clearly and solve problems (b) had a little difficulty (c) had some difficulty (d) had a great deal of difficulty (e) unable to think or solve problems?	○ a ○ b ○ c ○ d ○ e ○ Don't know ○ Refused

10. PAIN AND DISCOMFORT

39.	Have you had any trouble with pain or discomfort, during the past week?	○ Yes ○ No → **Go to 41** ○ Don't know ○ Refused
40.	How many of your activities, during the past week, were limited by pain or discomfort: none, a few, some, most, all?	○ None ○ A few ○ Some ○ Most ○ All ○ Don't know ○ Refused
41.	Overall, how would you rate your health during the past week? (a) excellent (b) very good (c) good (d) fair (e) poor	○ a ○ b ○ c ○ d ○ e ○ Don't know ○ Refused

For office use only:

Appendix M Health Utilities Index (HUI) For Children

Impacts of paediatric neuroinflammatory disorders on parents
Health Utilities Index (HUI) –Parent of Participant

Instructions:
The next set of questions asks about various aspects of (subject's name)'s overall health. When answering these questions we would like you to think about (his/her) health and ability to do things on a day-to-day basis, during the past week. To define the 1 week period, please think about what the date was 7 days ago and recall the major events that (he/she) has experienced during this period. Please focus your answers on (subject's name)'s abilities, disabilities and how they have felt during the past week.

You may feel that some of these questions do not apply to (subject's name), but it is important that we ask the same questions about each subject. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about (subject's name) abilities and feelings.

---

11. VISION

12. 1. 13. During the past week, has (subject's name) been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?

14. ○ Yes → **Go to 4**
15. ○ No
16. ○ Don't know
○ Refused

2. Has (subject's name) been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?

○ Yes → **Go to 4**
○ No
○ Don't know/ Didn't wear glasses or contact lenses
○ Refused

3. During the past week, has (subject's name) been able to see at all?

○ Yes
○ No → **Go to 6**
○ Don't know
○ Refused

4. During the past week, has (subject's name) been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?

○ Yes → **Go to 6**
○ No
○ Don't know
○ Refused

5. Has (subject's name) been able to see well enough to recognize a friend on the other side of the street *with* glasses or contact lenses?

- ○ Yes
- ○ No
- ○ Don't know/ Didn't wear glasses or contact lenses
- ○ Refused

17. HEARING

6. During the past week, has (subject's name) been able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

7. Has (subject's name) been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?

- ○ Yes → **Go to 9**
- ○ No
- ○ Don't know/ Didn't wear a hearing aid
- ○ Refused

8. During the past week, has (subject's name) been able to hear at all?

- ○ Yes
- ○ No → **Go to 11**
- ○ Don't know
- ○ Refused

9. During the past week, has (subject's name) been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?

- ○ Yes →**Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

10. Has (subject's name) been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?

- ○ Yes
- ○ No
- ○ Don't know/ Didn't wear a hearing aid
- ○ Refused

18. SPEECH

11. During the past week, has (subject's name) been able to be understood *completely* when speaking his/her own language with people who do not know (subject's name)?

- ○ Yes →**Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

12. Has (subject's name) been able to be understood *partially* when speaking with people who do not know (subject's name)?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

13. During the past week, has (subject's name) been able to be understood *completely* when speaking with people who know (subject's name) well?
- ○ Yes →**Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

14. Has (subject's name) been able to be understood *partially* when speaking with people who know (subject's name) well?
- ○ Yes →**Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

15. During the past week, has (subject's name) been able to speak at all?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

19. GETTING AROUND

16. During the past week, has (subject's name) been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?
- ○ Yes →**Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

17. Has (subject's name) been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?
- ○ Yes →**Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

18. Has (subject's name) been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?
- ○ Yes →**Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

19. During the past week, has (subject's name) been able to walk at all?
- ○ Yes
- ○ No → **Go to 22**
- ○ Don't know
- ○ Refused

20. Has (subject's name) needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

21. Has (subject's name) needed the help of another person to walk?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

22. Has (subject's name) needed a wheelchair to get around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

23. Has (subject's name) needed the help of another person to get around in the wheelchair?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

20. HANDS AND FINGERS

24. During the past week, has (subject's name) had the *full use* of both hands and ten fingers?
- ○ Yes →**Go to 28**
- ○ No
- ○ Don't know
- ○ Refused

25. Has (subject's name) needed the help of another person because of limitations in the use of his/her hands or fingers?
- ○ Yes
- ○ No → **Go to 27**
- ○ Don't know
- ○ Refused

26. Has (subject's name) needed the help of another person with some tasks, most tasks, or all tasks?
- ○ Some tasks
- ○ Most tasks
- ○ All tasks
- ○ Don't know
- ○ Refused

27. Has (subject's name) needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of his/her hands or fingers?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

21. SELF-CARE

28. During the past week, has (subject's name) been able to eat, bathe, dress and use the toilet without difficulty?
- ○ Yes →**Go to 31**
- ○ No
- ○ Don't know
- ○ Refused

29. Has (subject's name) needed the help of another person to eat, bathe, dress or use the toilet?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

30. Has (subject's name) needed special equipment or tools to eat, bathe, dress or use the toilet?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

22. FEELINGS

31. During the past week, has (subject's name) been feeling happy or unhappy?
- ○ Happy
- ○ Unhappy→**Go to 33**
- ○ Don't know
- ○ Refused

32. Would you describe (subject's name) as having felt:
(a) happy and interested in life, or
(b) somewhat happy?
- ○ a → **Go to 34**
- ○ b → **Go to 34**
- ○ Don't know
- ○ Refused

33. Would you describe (subject's name) as having felt:
a) somewhat unhappy
b) very unhappy
c) so unhappy that life was not worthwhile?
- ○ a
- ○ b
- ○ c
- ○ Don't know
- ○ Refused

34. During the past week, did (subject's name) ever feel fretful, angry, irritable, anxious or depressed?
- ○ Yes
- ○ No → **Go to 37**
- ○ Don't know
- ○ Refused

35. How often did (subject's name) feel fretful, angry, irritable, anxious or depressed:
rarely, occasionally, often, or almost always?
- ○ Rarely
- ○ Occasionally
- ○ Often
- ○ Almost always
- ○ Don't know
- ○ Refused

36. During the past week did (subject's name) feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

23. MEMORY

37. How would you describe (subject's name)'s ability to remember things, during the past week:
(a) able to remember most things
(b) somewhat forgetful
(c) very forgetful
(d) unable to remember anything at all?

○ a
○ b
○ c
○ d
○ Don't know
○ Refused

24. THINKING

38. How would you describe (subject's name)'s ability to think and solve day to day problems, during the past week:
(a) able to think clearly and solve problems
(b) had a little difficulty
(c) had some difficulty
(d) had a great deal of difficulty
(e) unable to think or solve problems?

○ a
○ b
○ c
○ d
○ e
○ Don't know
○ Refused

25. PAIN AND DISCOMFORT

39. Has (subject's name) had any trouble with pain or discomfort, during the past week?

○ Yes
○ No → **Go to 41**
○ Don't know
○ Refused

40. How many of (subject's name)'s activities, during the past week, were limited by pain or discomfort:
none, a few, some, most, all?

○ None
○ A few
○ Some
○ Most
○ All
○ Don't know
○ Refused

41. Overall, how would you rate (subject's name)'s health during the past week?
(a) excellent
(b) very good
(c) good
(d) fair
(e) poor

○ a
○ b
○ c
○ d
○ e
○ Don't know
○ Refused

For office use only:

Appendix N Resource Use Questionnaire

Resource Use Questionnaire –Neuroinflammatory Disorder (ND)

Introduction

Enter child ID. If the interview started face-to-face and was continued over the phone, please check both “Face-to-face” and “Telephone” options for question 0.5.	0.1 Participant ID: _____ 0.2 Interviewer: _____ 0.3 Date interview was completed: _____/___ / yyyy mm 0.4 Interview mode (*check all the apply*): □ 0. Face-to-face

The **primary caregiver** is the person primarily responsible for the care and upbringing of a child. **The equal caregiver** is two persons (a father and a mother) equally responsible for the care and upbringing of a child. **The secondary caregiver** is the second most responsible for the care and upbringing of a child.	□ 1. Telephone □ 2. Parent self completion 0.5 Date of child's birth: _____/___ / yyyy mm 0.6 Your relationship to the child (*check one*): □ 0. Mother □ 1. Father □ 2. Other (*please specify*): 0.6.A _____ 0.7 Which best describes your role in the child's care. I am the……. □ 0. Primary caregiver □ 1. Equal caregivers (equal responsibilities) □ 2. Secondary caregiver □ 3. Other (please specify): 0.7.A _____ 0.8 Have you or your child or another member of your household be diagnosed with the COVID-19? □ 0. No (→ skip to question 1.1) □ 1. Yes, tested positive. □ 2. Not applicable 0.9 If yes, who? □ Father □ Mother □ Sibling □ Other _____

Time Associated with Treatment and Care

Ask the parent to approximate the number of days the parent missed paid employment or usual daytime activities due to caring for their child with	1.1	Over a one year period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, on average, approximately how many days did you miss paid employment or your usual daytime activities (routine activities such as household activities, caring for other children, volunteering, attending school, etc.) because

the neuroinflammatory disorders **before the COVID-19 pandemic began in March 2020** and check the most applicable option. If "other", <u>specify the unit of time</u> in the text field.		you had to care for your child with ND? Please include personal / sick / vacation leave, and any time you took to bring the child to appointments or services related to his/her ND. ☐ 0. No days missed/Not applicable ☐ 1. Cannot recall ☐ 2. Prefer not to answer ☐ 3. 1 to 5 days ☐ 4. 6 to 10 days ☐ 5. 11 to 15 days ☐ 6. 16 to 20 days ☐ 7. 21 to 25 days ☐ 8. 26 to 30 days ☐ 9.Other (please specify): _____
Ask the parent to approximate the number of days <u>their spouse/partner or other caregiver</u> missed paid employment or usual daytime activities due to caring for their child with neuroinflammatory disorder before the COVID-19 pandemic began in March 2020 and check the most applicable option. If "other", <u>specify the unit of time</u> in the text field.	1.2	Over a one-year period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, on average, approximately how many days did your spouse/partner, or another caregiver miss <u>paid employment or their usual daytime activities</u> (routine activities such as household activities, caring for other children, volunteering, attending school, etc.) because they had to care for your child with ND? Please include personal /sick / vacation leave, and any time they took to bring the child to appointments or services related to his/her ND. ☐ 0. No days missed/Not applicable ☐ 1. Cannot recall ☐ 2. Prefer not to answer ☐ 3. 1 to 5 days ☐ 4. 6 to 10 days ☐ 5. 11 to 15 days ☐ 6. 16 to 20 days ☐ 7. 21 to 25 days ☐ 8. 26 to 30 days ☐ 9. Other (please specify):_____

Select <u>all that apply</u>.	1.3 Over a one-year period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, was your job/paid employment status affected by having a child with ND? *Please check all options that apply*: ☐ 0. No change/Not applicable ☐ 1. Change in employment status (e.g. from full-time to part-time or to another job) ☐ 2. Quit job ☐ 3. Reduced hours at work ☐ 4. Increased hours at work ☐ 5. Used sick days or vacation time to provide care for child ☐ 6. Took unpaid leave ☐ 7. Other (*please explain*): _____
Select <u>all that apply</u>.	1.4 Over a one-year period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, was your spouse/partner or another caregiver's job/paid employment status affected by having a child with ND? *Please check all options that apply*: ☐ 0. No change/Not applicable ☐ 1. Change in employment status (e.g. from full-time to part-time or to another job) ☐ 2. Quit job ☐ 3. Reduced hours at work ☐ 4. Increased hours at work ☐ 5. Used sick days or vacation time to provide care for child ☐ 6. Took unpaid leave ☐ 7. Other (*please explain*): _____

Mental Health Service Uses by Parents

2.11 Providing care for a child with significant needs can be stressful. Over a one-year period, from February 2019 to February 2020, before the COVID-19 began in March 2020, did you use services for yourself or your own mental health concerns because of increasing stress or pressure related to caregiving responsibilities for this child? Services may include visits with a family physician, mental health counsellors or therapists.

□ 0. No (→ *skip to question 2.18*)
□ 1. Yes (please provide details for each service below)
□ 2. Cannot recall (→ skip to question 2.18)
□ 3. Prefer not to answer (→ skip to question 2.18)

Ask in the period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, about how many of each of the services listed did you use over because of increased stress or pressure-related to caregiving responsibilities for this child and check the most applicable option.					
2.12 Health professional/service	**2.13 # Number of services used over one-year period**	**2.14 Was the cost of this service covered, totally or in**	**2.15 Over one-year period, from February 2019 to February 2020, before the COVID-19 began in March 2019,**	**2.16 Out-of-pocket costs (after any reimbursement)**	**2.17 Did this service's use changes after the COVID-19 pandemic**

		part, by a benefits plan? (circle one)	**were there any out-of-pocket costs for this service after any reimbursement?**		**began in March 2020?**
1. Family Physician	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15				0. No Change 1. Increase 2. Decrease
2. Social Worker	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
3. Psychologist	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
4. Psychiatrist	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

5. Family and Marriage Counsellor	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
6. Family Service Agency Visit (s) (Please specify the name of the organization)_____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
7. Walk-In Counselling Center Visit (s) (Please specify the name of the Center) _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
8. Mental health counselling from any other organization (please specify the name of the organization (s) _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

9. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga. Please specify the name of the service (s).	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
10. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga. Please specify the name of the service (s).	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
11. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga. Please specify the name of the service (s).	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

2.18 Providing care for a child with significant needs can be stressful. Over a one-year period, from February 2019 to February 2020, before the COVID-19 began in March 2020, did your spouse or partner use services for mental health concerns because of increasing stress or pressure related to caregiving responsibilities for this child? Services may include visits with a family physician, mental health counsellors or therapists.

□ 0. No (→ *skip to question 3.11*)
□ 1. Yes (please provide details for each service below)
☐ 2. Cannot recall (→ skip to question 3.11)
☐ 3. Prefer not to answer (→ skip to question 3.11)

Ask the parent in the period, from February 2019 to February 2020, before the COVID-19 pandemic began in March 2020, about how many of each services listed below did his/her spouse or partner use because of increased stress or pressure-related to caregiving responsibilities for this child with neuro inflammatory disorder and check the most applicable option.					
2.19 Health professional/service	**2.20 # Number of services used over one-year period**	**2.21 Was the cost of this service covered, totally or in part, by a benefits plan?**	**2.22 Over a one-year period, from February 2019 to February 2020, before the COVID-19 began in March 2019, were there any out-of-pocket costs for your spouse or partner for this service after reimbursement?**	**2.23 Out-of- pocket costs (after any reimbursement)**	**2.24 Did this service's use by your spouse or partner changes after the COVID-19 pandemic began in March 2020?**

		(circle one)			
1. Family Physician	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15				0. No Change 1. Increase 2. Decrease
2. Social Worker	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

3. Psychologist	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
4. Psychiatrist	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
5. Family and Marriage Counselor	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

	☐ More than 15				
6. Family Service Agency Visit (s) (Please specify the name of the organization) _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
7. Walk-In Counselling Center Visit (s) (Please specify the name of the Center) _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
8. Mental health counselling from any other organization (please specify the name of the organization (s))	☐ No one ☐ 1 to 5	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase

_____	☐ 6 to 10 ☐ 11 to 15 ☐ More than 15				2. Decrease
9. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga. Please specify the name of the service (s). _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease
10. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga. Please specify the name of the service (s). _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

11. Other Service(s) for mental health support specifically related to your caregiving, e.g., stress reduction, mindfulness, yoga, etc.). Please specify the name of the service (s). _____	☐ No one ☐ 1 to 5 ☐ 6 to 10 ☐ 11 to 15 ☐ More than 15	Yes/No	Yes/No	$ _____ per visit	0. No Change 1. Increase 2. Decrease

3. Prescription Medications(Pre-COVID 19)

3.11 Over six months, from September 2019 to February 2020 before the COVID-19 pandemic began in March 2020, **was any medication prescribed to you** to help with stress related to caregiving demands or worsened by caregiving demands?

- ☐ 0. No (→ *skip to question 3.21*)
- ☐ 1. Yes
- ☐ 2. Cannot recall (→ skip to question 3.21)
- ☐ 3. Prefer not to answer (→ skip to question 3.21)

3.12 If yes, are you taking it as prescribed? (→ skip to question 3.21)

0. No

1. Yes (*please provide details below*)

3.13 Name of medication	**3.14 Drug Identification Number (DIN)**	**3.15 Dosage strength (e.g., mg per tablet)**	**3.16 Number of months medication taken over last six months period, from September 2019 to February 2020, before the pandemic began in March 2020**	**3.17 Is the cost of this medication covered, totally or in part, by a drug plan?**	**3.18 Over a six months period, from September 2019 to February 2020, before the COVID-19 began in March 2019, were there any out-of-pocket costs for this medication (if not fully covered by a drug plan)**	**3.19 Out-of-pocket costs (after any reimbursement)**	**3.20 Did this medication's use changes after the COVID-19 pandemic began in March 2020?**
1.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease

2.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
3.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
4.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
5.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease

3.21 Over the six months from September 2019 to February 2020 before the COVID-19 pandemic began in March 2020, was any **medication prescribed to your spouse or partner** to help with stress related to caregiving demands or worsened by caregiving demands?

□ 0. No (→ end of questionnaire)
□ 1. Yes
□ 2. Cannot recall (→ end of questionnaire)
□ 3. Prefer not to answer (→ end of questionnaire)

3.22 If yes, are you taking it as prescribed?

0. No (→ end of questionnaire)

1. Yes (*please provide details below*)

3.23 Name of medication	**3.24 Drug Identification Number (DIN)**	**3.25 Dosage strength (e.g., mg per tablet)**	**3.26 Number of months medication taken over six months period, from September 2019 to February 2020, before the COVID-19 pandemic began in March 2020**	**3.27 Is the cost of this medication covered, totally or in part, by a drug plan?**	**3.28 Over a six months period, from September 2019 to February 2020, before the COVID-19 pandemic began in March 2019, were there any out-of-pocket costs for your spouse or partner for this medication (if not fully covered by a drug plan)?**	**3.29 Out-of-pocket costs (after any reimbursement)**	**3.30 Did this medication's use by your spouse or partner changes after the COVID-19 pandemic began in March 2020?**

1.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
2.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
3.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease
4.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease

5.			# months ____	Yes/No	Yes/No	$ _____ /month	0. No Change 1. Increase 2. Decrease

Appendix O Carer-related Quality Appendix Pof Life Questionnaire

Impacts of paediatric neuroinflammatory disorders on parents

CarerQoL Questionnaire

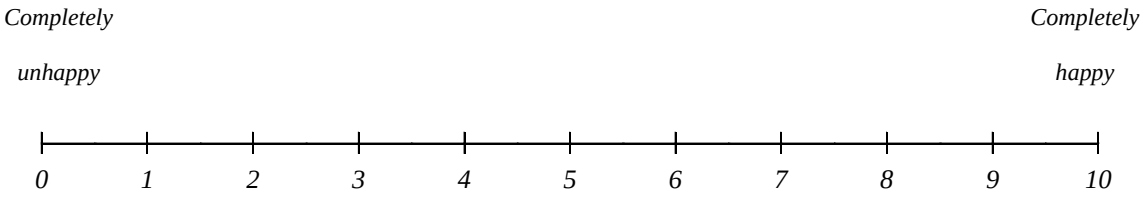
CarerQol-7D

Please draw an "X" to indicate which description best fits your current care giving situation

		no	some	a lot of	
a.	I have	☐	☐	☐	fulfillment with carrying out my care tasks.
b.	I have	☐	☐	☐	relational problems with the care receiver *(e.g., he/she is very demanding, he/she behaves differently, we have communication problems)*.
c.	I have	☐	☐	☐	problems with my own mental health *(e.g., stress, fear, gloominess, depression, concern about the future)*.
d.	I have	☐	☐	☐	problems combining my care tasks with my daily activities *(e.g., household activities, work, study, family and leisure activities).*
e.	I have	☐	☐	☐	financial problems because of my care tasks.
f.	I have	☐	☐	☐	support with carrying out my care tasks, when I need it *(e.g., from family, friends, neighbors, acquaintances)*.
g.	I have	☐	☐	☐	problems with my own physical health *(e.g., more often sick, tiredness, physical stress)*.

CarerQol-VAS

Please draw an "X" on the scale below to indicate how happy you feel currently



Completed by: _____ Date: _____

Appendix Q Previous protocol for capturing family spillover effects in randomized controlled trials (RCT)

Objective 3: To compare the incremental cost to standard care per QALY gained in CUAs estimated with and without the inclusion of health and cost spillover effects

For objective 3, analyses will be performed using a two-stage approach. First, a CUA will examine the difference in mean costs per child between treatment and control groups per QALY gained. A CUA will be conducted following the CADTH Guidelines for Economic Evaluations of Health Technologies for conducting a cost-utility analysis and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) (CADTH, 2017; Husereau et al., 2013).

<u>Objective 3.1:</u> To compare the incremental cost of metformin +physiotherapy to standard care per QALY gained in CUAs estimated with and without the incorporation of health and costs spillover effects on the parents of children with CP and evaluate how the conclusion may change when the spillover effects are included in the CUA.

Study Design

A CUA will be conducted using the patient-level data from a double-blind randomized placebo-controlled clinical trial (RCT) comparing metformin + physiotherapy to placebo + physiotherapy (usual care) for children with bilateral spastic CP aged 5 to 12 years. The RCT will take place at the Hospital for Sick Children (SickKids), and Holland Bloorview Kids Rehabilitation Hospital (HBKR). Recruitment will occur over 2020-2023. The aims of this phase II RCT study are to assess tolerability and safety of metformin, to establish trial feasibility, and to collect preliminary efficacy for a larger multi-center phase III RCT study.

The experimental intervention for this study is metformin + physiotherapy. Children with CP face a lifetime motor impairment, some of which can be treated with physiotherapy. Recent findings from rodent models suggest that type II diabetes drug metformin can promote brain repair and motor improvements (Dadwal et al., 2015; Wang et al., 2012). For this study, researchers want to determine whether taking the drug metformin for 16 weeks while doing physiotherapy leads to better gross motor function and thinking skills in children with CP compared to physiotherapy +placebo (usual care).

In the second stage of the analysis, health and costs spillovers on parents of children with bilateral spastic CP will be incorporated into the CUA using the theoretical framework for incorporating family spillover effects in paediatric economic evaluation (from the primary objective). A working theoretical framework for including family spillover effects can be found in Appendix A. Finally, a comparative analysis of the results from the first stage (conventional CUA) and second stage (CUA with the incorporation of health and costs spillover effects) will be conducted.

Study Population

The target population is children diagnosed with bilateral spastic CP aged 5 to 12 years and their parents (or caregivers).

Sample Size

The double-blind controlled randomized trial will enroll 50 children with bilateral spastic CP aged 5 to 12 years and their parents (or caregivers) at The Hospital for Sick Children (Sick Kids) and Holland Bloorview Kids Rehabilitation Hospital (HBKR). The children with bilateral spastic CP will be randomized to receive metformin + physiotherapy or placebo + physiotherapy (25 per group).

Assessments

The assessment will be performed at baseline and 16 weeks after randomization. The demographic questionnaire will be administered at the baseline. The Resource Use Questionnaire (RUQ-CP), HUI (for children with CP and their parents (the respondent), CarerQoL, and other measures will be administered at baseline and 16 weeks.

Comparators

The intervention group is children receiving physiotherapy + metformin and their parents (or caregivers). The control group is children receiving placebo+ physiotherapy group and their parents (or caregivers). Both groups will receive active physiotherapy for 16 weeks. Sessions will occur twice weekly for approximately 45 minutes per session. All participants will start at 250 mg (half a tablet), which will be taken by mouth or via a gastrostomy tube once daily during Week 1. At the end of Week 1, if metformin is well-tolerated, and there are no medical concerns, the dose will be increased to 250 mg (half a tablet) twice daily and taken during Week 2. At the end of Week 2, if the drug is well tolerated and there are no medical concerns, for participants with a body surface area (BSA) range of 0.63 to 1.12, the dose will increase up to 500 mg twice

a day, according to the dosing nomogram and individual BSA. This increased dose will be taken from Weeks 3-16. For participants with a BSA higher than 1.12, the dose will be increased to 500 mg twice a day during Week 3. At the end of Week 3, if the dose is well tolerated and there are no medical concerns, the dose for participants with a BSA greater than 1.12 will be increased up to 1000 mg twice a day based on the dosing nomogram and each participant's BSA range. This increased dose will be taken from Weeks 4-16. Doses will be rounded to increments of half tablets (250 mg, 500 mg, 750 mg, and 1000 mg). If the participant is experiencing any adverse events, at the discretion of a delegated study physician, the dosage will be decreased in multiples of 250 mg or discontinued. Once the adverse event has been resolved, and there is no longer a medical concern, a delegated study physician can re-initiate or increase the dosage in multiples of 250 mg, not exceeding the maximal dosage outlined for the individual's baseline BSA up to 1000 mg twice a day. All participants will be advised to take any commercially available daily children's multivitamin that contains cyanocobalamin (Vitamin B12) over the duration of the study.

Perspective

The public healthcare payer and societal perspectives (for the reference case analysis) will be taken. The CADTH recommends reporting a reference case from a publicly funded healthcare payers' perspective, which includes costs incurred by Canadian public payers and health effects for patients and their informal caregivers (CADTH, 2017).

Time Horizon and Discounting

The time horizon of this analysis will be 16 weeks to coincide with the study period. No discounting on health outcomes and costs will be applied.

Valuing Outcomes

The primary health outcomes are the preference-based HRQoL of children and their parents (the respondent). The health-related QoL of children with CP and their parents (the respondent) will be measured using the HUI. The interviewer-administered self-assessed and proxy versions are already included in the RCT. For children under 8 years of age, and for older children with more severe disability, cognitive impairments or communication difficulties, the parent proxy version of HUI will be used. The interviewer-administered self –assessment version of the HUI for adults has been added to the study to measure parental health spillover effects and will permit the calculation of health utility scores. Measuring health outcomes using HUI for both the patient

(child with bilateral spastic CP) and the parent will allow combining health utility for the child and the caregiver to conduct a CUA of metformin+ physiotherapy compared to usual care that includes health spillover effects on the parent. The HUI for children with CP and their parents will be administered by interview at baseline and 16 weeks. A one-week recall period will be used. With the assumption that life expectancy will be unchanged over the 16 weeks of the study period, the health utility weights from the HUI-III will be used to determine the number of QALYs for each participant (children and their parents). The HUI-III was chosen because it has a complete descriptive system of the two systems, full structural independence, and population norms available compared to HUI-II (Horsman et al., 2003). HUI-II does offer distinct, independent attributes, including self-care, the emotion that focuses on worry/anxiety, and fertility. The HUI-3 scoring system provides health-state values that correspond to a classification system comprising eight domains (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), with between four and six levels within each domain. Multi-attribute utility function will be used to convert comprehensive health state description into preference measures of overall HRQoL (Horsman et al., 2003). The QALYs will be calculated by applying the area-under-the-curve (AUC), which is calculating the AUC based on the area defined by the change from baseline utility Manca et al., 2005). The detail description on QALY calculation is described below (section…).

Costing

Direct and indirect costs related to the treatment of children with CP will be measured using the parent-administered Resource Use Questionnaire (RUQ-CP) developed and modified for the study and patient population by Dr. Wendy Ungar and her team. The RUQ-CP assess each family's use of healthcare, educational, social, and personal resources related to caring for a child with CP. Direct costs includes direct healthcare costs (medications, physiotherapy, physician services, medical procedures, imaging, inpatient care, emergency department, ambulance, home care, complementary medicine, non-prescription medications, and other health services, including treatment of drug and disease-related adverse events) and direct non-health costs (cost related to CP-resources used in education, community services, social services and child & youth service sectors). Indirect costs include times losses incurred by parents (and/or caregivers) from paid and unpaid labour due to caregiving responsibilities for children with CP and mental health service use by parents (and/or caregivers). The original RUQ-CP was modified

to include mental health service use by parents. Questions about mental health service use include a list of mental health counsellors including a family physician, social worker, psychologist, family and marriage counselor, and mental health service providers, including family service agency, walk-in counselling, and medications used by parents to help with stress-related to caregiving. Recall periods of 4 months will be used for baseline and 16 weeks of assessments.

Prices will be assigned to each resource use items using Canadian sources. Prices will be obtained from institutions, the Ontario Health Insurance Program fee schedule, the Ontario Drug Benefits formulary, and published resources. For emergency department and inpatient care, patient-level costs for the most responsible diagnosis related to CP will be obtained from the Ontario-Case Costing Initiative (OCCI) and the Canadian Institute for Health Information (CIHI) patient cost estimator interactive tool. The costs of parent/caregiver time losses will be estimated using a human capital approach, where the estimated volume of lost productivity time, up to 8 hours per day, will be multiplied by average hourly Canadian age-and sex-specific wage statistics (StatisticsCanada, 2018). Costs from earlier years will be adjusted using the health care component of the Consumer Price Index, and all the costs will be calculated in Canadian dollars ($CAD) in 2020 prices.

Imputation of missing values

Missing data for costs and effects will be imputed using several strategies that were used in previous CEA studies (Feenstra, Hamberg-van Reenen, Hoogenveen, & Rutten-van Molken, 2005; Noble, Hollingworth, & Tilling, 2012; Smit, Evers, de Vries, & Hoving, 2013). Missing data for costs and HUI questions may be imputed using mean imputation, using respondents' scores on the previous and next measurements or using the last observation carried forward technique (LOCF) Naeim, Keeler, & Mangione, 2005). Mean imputation followed by LOCF is a common approach to replace missing data in trial-based CEAs with incomplete observations (Leurent, Gomes, & Carpenter, 2018; Noble et al., 2012). Unrealistic values (e.g. parents' visits to the family physician or missed paid employment in the last 4 months) will be imputed with the highest realistic value.

Analysis

Descriptive analyses of the demographic characteristics of children with CP and their parents will be conducted. Descriptive statistics will be reported in percentages and mean (standard deviations) where applicable.

A total cost per child from the perspectives of the public health care payer and of society will be reported for baseline and 16 weeks for each group. The total cost per child from a publicly funded healthcare payers perspective will be obtained by summing appropriate direct costs incurred by Canadian public payer including medications, physiotherapy, physician services, medical procedures, imaging, inpatient care, emergency department, ambulance, home care, complementary medicine, non-prescription medications, and other health services, including treatment of drug and disease-related adverse events) and direct non-health costs (cost related to CP-resources used in education, community services, social services and child & youth service sectors). A total cost per child from a societal perspective will be determined by summing direct costs (as described for Canadian public payer) and indirect costs, including costs related to productivity loss by parents and out of pocket costs. The mean costs per parent for mental health services use costs by parents to cope with stress stemming from caregiving responsibilities or having a child with chronic illness or disability will be reported separately for both treatment and control group. The mean costs per child from a publicly funded healthcare and societal perspectives will be reported for the baseline and 16 weeks for treatment and control groups.

The mean HUII-III health utility and domains scores for children with CP and their parents will be reported for baseline and 16 weeks for each group. The caregiver burden measured with the CarerQoL instrument will also be reported in mean (with standard deviation) at baseline and 16 weeks. The difference in baseline characteristics (parent and child) between treatment and control group will be tested using t-tests or other appropriate tests (Vickers, 2005). Similarly, observed differences in mean scores (of health utility scores for parents and children, total cost per child from publicly funded healthcare payers and societal perspectives, and CarerQoL) between treatment and control groups at baseline and 16 weeks will be tested with t-tests or Kruskal–Wallis or Mann–Whitney tests for non-normally distrusted data. A significance value (P-value) and 95% Confidence Interval (CI) of the difference is reported.
First, an incremental cost-utility ratio (ICUR) will be calculated using patient-level RCT-data from the public health care payer perspective (reference case) and societal perspective. The

ICUR is the ratio between the difference in mean costs and the difference in mean QALYs between treatment and control groups. The change from the baseline approach will be used for calculating differential mean costs and QALYs between groups (Manca, Hawkins, & Sculpher, 2005). This approach will allow addressing imbalances in mean baseline health utility and costs between trial arms and usually reduces the random variation. For instance, for the health utility calculation, instead of using the absolute health utility value at follow up to calculate an individual's QALYs, this approach uses the difference between baseline and follow-up health utility. For each patient, the change in health utility and costs will be calculated by subtracting the baseline health utility and costs from 16 weeks follow up for treatment and control groups. The QALYs will be calculated by applying the area-under-the-curve (AUC), which is calculating the AUC based on the area defined by the change from baseline utility (Manca et al., 2005). The measure of treatment effect will be obtained as the difference in the mean change in QALYs in alternative arms of trial rather than the difference in mean absolute QALYs. Instead of using the absolute utility value at follow up to calculate an individual QALYs', the difference in mean methods use the difference between baseline and follow-up utility. For instance,

$$\Delta QALYs_{treatment} = (health\,utility_{\,follow\,up} - health\,utility_{\,baseline}) * lifeyears \ldots\ldots (9)$$

The incremental costs will be estimated by subtracting the differential mean costs of the treatment group from the differential mean costs of the control group.

$$ICUR = \frac{[(Cost_{treatment16weeks} - Cost_{treatment\ baseline}) - (Cost_{control16weeks} - Cost_{control\ baseline})]}{(\Delta QALYs_{treatment} - \Delta QALYs_{control})} \ldots \ldots \ldots (1$$

$$ICUR = \frac{(\Delta Cost_{treatment} - \Delta Cost_{control})}{(\Delta QALYs_{treatment} - \Delta QALYs_{control})} \ldots \ldots \ldots (11)$$

Second, an ICUR will be estimated by incorporating health spillover effects (health utility score measured by HUI-III on parents and costs of mental health service uses by parents to cope with stress stemming from caregiving responsibilities or having a child with chronic illness or disability. The mean family health utility scores will be derived using the theoretical framework developed for the primary objective and be applied to the child's life years for QALY calculation. For instance, family health utility in a two-person household consists of a child with CP and his/her primary caregiver (a mother or father or the respondent-caregiver).

$$U_f = U\ (H_r, H_c, Z) \ldots \ldots \ldots (11)$$

Where, U_f is family health utility in period t, H_r, and H_c are the health utilities of a primary caregiver (the respondent (a mother or father or caregiver), and a child with CP living in a two-person household, and Z is vector of externalities that impacts a child and primary caregiver health. The QALYs can be obtained by multiplying U_f by a child's life expectancy.

The estimated ICUR with health spillover effects on the parent of children with CP will be compared with estimated ICURs from the public health care payer perspective (reference case) and societal perspective that does not include incorporation of parent health spillover effects and parent's mental health services use costs. Finally, the estimated ICURs will be compared with the commonly used ICER threshold for Canada of $20 000 to $100 000 per QALY gained (Laupacis et al., 1992).

Uncertainty Analysis

In addition to a deterministic analysis described above, and a probabilistic analysis (PA) will be conducted to check the robustness of results for variations in underlying assumptions regarding structural and parameter uncertainty (Hatswell, Bullement, Briggs, Paulden, & Stevenson, 2018; Jain, Grabner, & Onukwugha, 2011). The variables that will be varied in one-way sensitivity analysis include placebo+ physiotherapy and metformin + physiotherapy effectiveness, base case estimates of health resource use for costly items, cost of metformin, and productivity losses by parents. The results of one-way sensitivity analyses will be depicted in the tornado diagram. For PSA, means, standard deviation and distributions (e.g. normal, beta, gamma. Log-normal) will be determined for costs and outcome variables from patient-level data from CP study. The PSA will be conducted using Monte Carlo methods, which involves running the model many times using randomly sampled values of the model input. The PSA allows calculating the 95% confidence intervals around the incremental costs and the incremental effectiveness measures. Cost-effectiveness acceptability curves will be estimated to indicate the intervention' probability of being cost-effective compared with others at different values of willingness-to-pay through Monte Caro Simulation.

<u>Objective 3.2</u> To compare the incremental cost of metformin to standard care per QALY gained in CUAs estimated with and without the incorporation of health and costs spillover effects on parents of children with MS and examine how the conclusion may change when the spillover effects are included in the CUA.

Study Design

For objective 3.2, a CUA will assess the economic benefit of the administration of metformin in children with MS compared to placebo. Similar to objective 3, analyses will be performed using a two-stage approach. First, a CUA will examine the differences in mean costs per child between treatment and control groups, per QALY gained without including the parent mental health cost and health spillover effects on parents of children with MS. A CUA will be conducted following guidelines from of CADTH Guidelines for Economic evaluations of Health Technologies for conducting a cost-utility analysis and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard (CHEERS (CADTH, 2017; Husereau et al., 2013). Second, the cost and health spillover effects on parents will be included using the developed theoretical framework for incorporating family spillover effects in paediatric economic evaluation (from primary objective) and conduct a CUA. Finally, the comparative analysis of CUAs with and without the health and costs spillover effects will be conducted.

This objective was added to the planned phase I double-blind study of metformin acting on endogenous neural progenitor cells in children with multiple sclerosis (MS). The CUA will be conducted using patient-level data from a randomized multiple baseline feasibility trial, where participants will be randomized to starting metformin at 3-months, 6 months, or 9 months into the study during the 12 months trial. The primary objectives of this RCT are 1) to determine the safety and tolerability of the use of metformin the population and 2) to determine the feasibility of the trial design.

Study Population

The target population is children diagnosed with MS aged 10 years to 18 years and 11 months and their parents (or caregivers).

Sample size

The study will enroll 30 children and their parents (or caregivers) through the Neuroinflammatory Disorders clinic at The Hospital for Sick Children (Sick Kids). The economic assessment will be performed at baseline, 6 month and 12-month follow-ups.

Assessments

The assessment will be performed at baseline, 6 months and 12-month follow-ups. The demographic questionnaire will be administered at the baseline. The Resource Use Questionnaire

(RUQ-ND), HUI (for children with CP and their parents (the respondent), CarerQoL, and other measures will be administered at baseline, 6 months and 12 months follow-ups.

Comparators

The intervention group is children receiving metformin and their parents. The control group is children receiving placebo and their parents. Since the study is RCT multiple baseline feasibility trial, all participants will receive the treatment-metformin and will be on a daily dose of metformin for a minimum of 3 months and a maximum of 9 months. Similarly, all participants will be on a daily dose of placebo for a minimum of 3 months and a maximum of 9 months. The same participants will be in the control group (placebo) before the administration of metformin and in the treatment group after the administration of metformin. The proposed dose and the schedule of administration of metformin/placebo will be based on safety and toxicity data obtained from previous use in paediatric population and animal studies (Sun, Wang, Zhang, & He, 2019; Wang et al., 2012). The metformin and placebo doses will be 500 mg/m2/day po (to be rounded) given in 1 or 2 divided doses for one week and if there are no side effects increased to 1000 mg/m2/day po given in 2 divided doses for the rest of the trial. Doses will be rounded to increments of half tablets (250mg, 500mg, 750mg, and 1000mg). At each visit, the subject's BSA will be checked, and the prescription provided will be adjusted as needed

Perspectives

The public healthcare payer and societal perspectives (for the reference case analysis) will be taken. The CADTH recommends reporting a reference case from a publicly funded healthcare payers' perspective, which includes costs incurred by Canadian public payers and health effects for patients and their informal caregivers (CADTH, 2017).

Time Horizon and Discounting

The time horizon of this analysis is 12 months. No discounting on health outcomes and costs will be applied.

Valuing health outcomes

The primary health outcome for the CUA will be preference based-health related (HRQoL) quality of life of children with MS and their parents (or caregivers). The preference-based HRQoL will be measured using the Health Utilities Index (HUI). The HUI interview proxy version for children with MS and the HUI interview self version for the parent has been added to the study. A one-week recall period will be used. With the assumption that life expectancy will

be unchanged over the 12 months of the study period, the health utility weights from the HUI-III will be used to determine the number of QALYs for each participant (children and their parents). Furthermore, CarerQoL has been added to measure the caregiver burden. The HUI and CarerQoL will be administered at baseline, 6-and 12-months follow-ups.

Costing

Direct and indirect costs related treatment of children with MS will be measured using the parent administered Resource Use Questionnaire (RUQ) developed population by Dr. Wendy Ungar her team (Tsiplova et al., 2019; W. J. Ungar et al., 2018). The RUQ assess each family's use of healthcare, educational, social, and personal resources related to caring for a child with CP. The RUQ for MS (discussed in objective #2) and RUQ-CP, expect the disease name, the CP was changed to MS where applicable. Prices will be assigned to each resource use using the same approach as described in objective #3.1. Costs from earlier years will be adjusted using the health care component of the Consumer Price Index, and all the costs will be calculated in Canadian dollars ($CAD) in 2020 prices.

Imputation

Missing data for costs and effects will be imputed using similar approaches described in section 1.2.2.9

Analysis

Descriptive statistics (mean, standard deviation (SD), percentage) will be reported for the child and parent demographic characteristics. The mean cost per child will be summarized by direct and indirect (costs spillover effects for parents) treatment (after the treatment) and control groups (before the treatment) where applicable. The mean (sample mean and standard deviation) health utility scores (HUI-III) for children with MS and their parents (health spillover effects) will be reported for baseline, 6- and 12-months follow-ups (where applicable). Furthermore, the caregiver burden measured with the CareQoL instrument will also be presented in mean (with standard deviation). Observed mean differences in mean scores (health utility scores and CarerQoL) before and after the treatment will be tested using t-tests or Kruskal–Wallis or Mann–Whitney tests for non-normally distrusted data.

Like the in secondary objective 2, first, an ICUR will be calculated using patient-level data from a randomized multiple baseline feasibility trial for children with MS. The analyses will be undertaken from the public health care payer perspective and societal perspective. The societal

perspective will include costs of productivity for the parent in addition to direct costs. The mean costs per child and QALYs per child will be used for the estimation of ICUR. There will be no need to adjust for baseline differences as the same participants will be in the control and treatment groups. Patient-level QALYs will be estimated by applying the AUC method, which is by summing the areas of the geometrical shapes obtained by linearly interpolating between health utility scores over the study period (Manca et al., 2005; Sassi, 2006).

$$ICUR = \frac{(Cost_{after\ the\ treatment} - Cost_{before\ the\ treatment})}{(QALYs_{after\ the\ treatment} - QALYs_{before\ the\ treatment})} \ldots\ldots(12)$$

Second, an ICUR will be estimated including health spillover effects on parents. The mean family health utility scores will be derived using the theoretical framework developed for the primary objective and will be applied to the child's life-year gained for QALY calculation. Finally, a comparative analysis will be conducted between estimated ICURs from the health care payer perspective, societal perspective and the inclusion of health spillover effects on parents. The estimated ICURs will be compared with the commonly used ICER threshold for Canada of $20 000 to $100 000 per QALY gained (Laupacis et al., .1992).

Uncertainty Analysis

The impact of uncertainty in key parameters on the CEA results will be assessed through a series of one-way deterministic and probabilistic sensitivity analyses (Hatswell et al., 2018; Jain et al., 2011). The variables that will be varied in one-way sensitivity analysis include metformin effectiveness (base case estimates of health resource use for costly items, cost of metformin, and productivity losses by parents. The results of one-way sensitivity analyses will be depicted in the tornado diagram. For PSA, means, standard deviation and distributions (e.g., normal, beta, gamma. Log-normal) will be determined for costs and outcome variables from patient-level data from CP study. The PSA will be conducted using Monte Carlo methods, which involves running the model many times using randomly sampled values of the model inputs. The PSA allows calculating the 95% confidence intervals around the incremental costs and the incremental effectiveness measures. Cost-effectiveness acceptability curves will be estimated to indicate the intervention' probability of being cost-effective compared with others at different values of willingness-to-pay through Monte Caro Simulation (Hatswell et al., 2018).