

# An Economic Evaluation of Teratology Information Services

by

Rebecca L Hancock

A thesis submitted in conformity with the requirements  
for the degree of Doctor of Philosophy

Institute of Medical Science  
University of Toronto

© Copyright by Rebecca L Hancock 2010

# An Economic Evaluation of Teratology Information Services

Rebecca L Hancock

Doctor of Philosophy

Institute of Medical Science  
University of Toronto

2010

## Abstract

### BACKGROUND

Teratology Information Services (TIS) educate the public and health professionals via telephone regarding the safety of drugs and other exposures during pregnancy and lactation. Currently TIS consultations are free, but funding is eroding. A cost-benefit analysis may inform resource allocation. It was hypothesized that an individual TIS consultation regarding anti-depressant use during pregnancy provides a positive net benefit compared to a family doctor (FD) consultation.

### METHODS

A survey of international TIS was conducted to gauge TIS costs. A discrete choice experiment (DCE) was designed to assess preferences and willingness-to-pay (WTP, an estimate of benefit) for teratology counseling. DCE respondents (local community volunteers) chose between potential counseling services following an anti-depressant exposure during pregnancy. Services were described by five service attributes and one cost attribute, which were generated in focus groups. Preferences and WTP were estimated using logit regression. Incremental benefits and costs of counseling by TIS and FD were compared in a probabilistic sensitivity analysis to obtain the incremental net benefit from both a societal (productivity costs included) and health system

perspective. The FD consultation was costed through OHIP billing codes. The TIS consultation was micro-costed.

## RESULTS

Eighteen TIS in North America and 16 international TIS completed the survey. Most TIS are small (median two employees, median budget US\$69,000). The DCE had 175 respondents. The most important attribute of counseling was receiving very helpful information; information delivery methods were less important. WTP for the TIS scenario was CDN\$124 (SD \$12); WTP for the FD scenario was CDN\$79 (SD \$8). Service costs were similar for TIS and FD (approximately \$32/consultation); FD had higher productivity costs. Incremental TIS benefits were likely to outweigh costs under both the societal and health system perspectives (probability 99% and 97% respectively).

## CONCLUSIONS

An economic evaluation of a program that delivers pregnancy health information via telephone required a novel approach. While there are some methodological challenges to valuing benefits through willingness-to-pay, it may be appropriate for valuing counseling. TIS should emphasize their ability to provide high quality information. The benefits of an individual TIS consultation on anti-depressant use during pregnancy are likely greater than the costs.

## Acknowledgments

I will be forever grateful to my supervisor, Wendy Ungar, for her incredible mentorship. She has been unfailingly generous with her time and energy, and has shared her passion for conducting high quality and meaningful research with me. I am very proud to have been her first PhD student.

I would also like to acknowledge the support of my thesis committee advisors. Gideon Koren has been incredible supportive and kind since I first worked as his master's student. Deborah Marshall's involvement in this work was vital. Her expertise in conjoint analysis was absolutely essential to this project. Michael Goodstadt provided his unique perspectives on the many issues we encountered through the years, and some of my best thinking occurred during our discussions over coffee. Adrienne Einarson's insights into maternal and child health, and vast experience in teratology research and programming, have been of great value. One could not ask for better teachers and friends.

Many colleagues in the Child Health and Evaluative Sciences and Clinical Pharmacology departments at the Hospital for Sick Children provided support to this project. I would like to thank Tom Einarson, David Fisman, Irina Nulman, and Andy Willan for peer-reviewing early protocols. I would also like to thank Andy Willan for his help with statistical trouble-shooting, along with Eshetu Atenafu and Derek Stephens. I would like to thank the Economics Department at City University for hosting me over the summer of 2007. I thank the counselors at Motherisk for training me to work with them at their phenomenal program, providing me with one of the richest learning experiences out of my many years in school. Their work is incredible and I am very grateful to have had the opportunity to be a part of it. I would also like to thank them for giving their time to the focus group discussions.

I would like to thank my colleagues at the Organization of Teratology Information Specialists, the European Network of Teratology Information Services, and TIS around the world for giving their time to complete the survey. I would like to thank the members of the public who volunteered their time to participate in focus groups and to fill out the discrete choice survey. I am always touched by people's willingness to contribute to research, out of a belief that they can

help improve the world in some small way. This work would not have been possible without them.

I wish to gratefully acknowledge the generous funding support of the Research Training Centre at the Hospital for Sick Children, the Organization of Teratology Information Specialists, and the Canadian Institutes for Health Research.

I have been the beneficiary of a wonderful personal support system. I want to thank my parents, Margaret Hancock and Ian Anderson, for their remarkable ability to be really genuinely interested in my thesis (if it was an act, you deserve Oscars), and for reading and commenting on numerous drafts, abstracts, and survey versions. Many friends also provided both concrete and intangible support by reading drafts and then chatting about other things. I would especially like to thank my partner, Curt Howard. Curt sets a personal example of professional integrity coupled with a strong work ethic that has provided me with the motivation needed to complete this project to the best of my abilities. His tremendous faith in me is a gift cherished beyond words.

# Table of Contents

Acknowledgments.....	iv
Table of Contents.....	vi
List of Tables .....	xi
List of Figures.....	xiii
List of Appendices .....	xiv
List of Appendices .....	xiv
1 Chapter 1: Introduction .....	1
1.1 Overview.....	1
1.2 Teratology Information Services .....	1
1.3 Effectiveness of TIS in Improving Maternal and Neonatal Outcomes.....	3
1.3.1 Prevention of congenital malformations.....	3
1.3.2 Prevention of unnecessary pregnancy termination .....	4
1.3.3 Support of optimal folate and vitamin supplementation to improve child health...	5
1.3.4 Support of optimal drug therapy during pregnancy .....	7
1.3.5 Prevention of Occupational Risks.....	8
1.3.6 Support of Breastfeeding .....	9
1.3.7 Knowledge Transfer and Translation.....	9
1.3.8 Reducing Anxiety and Correcting Risk Misperceptions .....	11
1.3.9 Conclusions from Literature Review of TIS Effectiveness .....	12
1.4 Introduction to Economic Evaluations and Utility Measurement in Health Economics ..	13
1.5 Economic Evaluations of Programs Promoting Health and Providing Counseling in Pregnancy.....	13
1.5.1 Costs of Birth Defects and Birth Defect Prevention.....	14
1.5.2 Prevention of Low Birth Weight.....	17
1.5.3 Improving Folic Acid Levels.....	18
1.5.4 Economic Evaluations of Other Pregnancy Outcomes.....	19
1.5.5 Economic Consequences of Investment in Child Health.....	19
1.6 Health Care Cost Savings Associated with TIS.....	21
1.7 Literature Review of Telephone-based Health Care.....	21
1.8 Challenges in Performing an Economic Evaluation of TIS.....	23

1.8.1	Selection Bias of TIS clients.....	23
1.8.2	Value of Information.....	24
1.8.3	Selection of a Comparator Program.....	24
1.8.4	Measurement of TIS Outcomes .....	24
1.9	Introduction to Conjoint Analysis and Discrete Choice Experiments .....	25
1.10	Introduction to Cost-Benefit Analysis .....	27
1.11	Statement of the Problem: Need for a Cost-Benefit Analysis of TIS .....	28
1.12	Study Rationale.....	29
1.13	Hypothesis and Research Objectives .....	30
1.14	Thesis Organization .....	30
2	Chapter 2: Survey of TIS .....	31
2.1	Introduction.....	31
2.1.1	Background and Rationale.....	31
2.1.2	Research Objectives.....	31
2.2	Methods.....	32
2.2.1	Study Design.....	32
2.2.2	Survey Participants and Sample Size.....	32
2.2.3	Recruitment of Survey Participants .....	32
2.2.4	Privacy and Confidentiality of Survey Participants.....	33
2.2.5	Informed Consent Process for Survey Participation.....	33
2.2.6	Development of the Survey Instrument .....	33
2.2.7	Data Collection .....	33
2.2.8	Data Analysis .....	33
2.3	Results.....	34
2.3.1	Services.....	36
2.3.2	Staffing.....	38
2.3.3	Operations.....	40
2.3.4	Data Collection and Research.....	45
2.3.5	Knowledge Transfer Activities .....	46
2.3.6	Additional Information .....	47
2.4	Discussion.....	48
2.4.1	Discussion of North American TIS Survey Data.....	48

2.4.2	Comparisons between North American and International TIS Survey Responses.....	51
2.4.3	Limitations .....	54
2.5	Conclusions.....	54
3	Chapter 3: Discrete Choice Experiment to Assess Public Preferences and Willingness to Pay for Teratology Counseling During Pregnancy .....	56
3.1	Introduction.....	56
3.1.1	Overview.....	56
3.1.2	Hypothesis and Objectives.....	57
3.2	Methods.....	57
3.2.1	Selection of Attributes and Levels.....	58
3.2.2	Selection of Experimental Design .....	72
3.2.3	Pilot Testing of the Survey Instrument.....	80
3.2.4	Measurement of Preferences.....	84
3.2.5	Data Management and Analysis .....	86
3.3	Results.....	93
3.3.1	Recruitment of Participants.....	93
3.3.2	Demographic Characteristics of Survey Respondents.....	94
3.3.3	Regression Models.....	98
3.3.4	Dominant and Illogical Decision Makers .....	107
3.3.5	Importance Scores versus Choice of Most Important Attribute .....	110
3.3.6	Comparison of Fixed Choice Task Responses to Utility for Specific Scenarios	111
3.3.7	Real Life Use of Information Sources .....	112
3.4	Discussion.....	113
3.4.1	Comparison of Demographic Characteristics of Sample with Greater Toronto Population .....	114
3.4.2	Preferences for Teratology Counseling .....	114
3.4.3	Influence of Demographic Factors on Preferences.....	116
3.4.4	Validity of Discrete Choice Experiments .....	118
3.4.5	Limitations and Methodological Issues .....	120
3.5	Conclusions.....	121

4	Chapter 4: Methodological Challenges in Using Willingness-to-Pay Estimates in a Cost-Benefit Analysis of a Teratology Counseling Encounter.....	123
4.1	Introduction.....	123
4.1.1	Overview of Cost-Benefit Analysis.....	123
4.1.2	Rationale.....	124
4.1.3	Objectives.....	125
4.2	Methods.....	125
4.2.1	Overview of Methodological Challenges.....	125
4.2.2	Cost-Benefit Analysis.....	126
4.2.3	Measurement of Benefits.....	127
4.2.4	Measurement of Costs for TIS.....	132
4.2.5	Measurement of Costs for Physician Services.....	136
4.2.6	Data Analysis and Probabilistic Sensitivity Analysis.....	137
4.2.7	Two Approaches to Estimating TIS Benefits: Model Uncertainty.....	139
4.2.8	Analysis from the Health Care System Perspective.....	139
4.3	Results.....	139
4.3.1	Results of the Probabilistic Sensitivity Analysis.....	139
4.3.2	Results of the Analysis under the Second Approach to TIS Benefits.....	144
4.3.3	Results of the Analysis from a Health Care System Perspective.....	145
4.4	Discussion.....	146
4.4.1	Summary of Key Findings.....	146
4.4.2	Discussion of Methodological Challenges.....	147
4.5	Conclusions.....	153
5	Chapter 5: General Discussion of Findings.....	154
5.1	Discussion of Main Findings.....	154
5.1.1	Teratology Counseling and Drug Safety Surveillance.....	155
5.1.2	Methodological Issues.....	156
5.1.3	Health Care Preferences.....	161
5.1.4	Applying the Health Belief Model to TIS.....	162
5.1.5	The Role of Risk Perception and Communication in TIS Utilization.....	163
5.1.6	Generalizability of Findings.....	164
5.1.7	Limitations.....	165

5.2 Conclusions.....	165
5.2.1 Implications for Stakeholders .....	166
5.2.2 Future Directions .....	169
References.....	171
Appendices.....	194

## List of Tables

Table 1: Estimates of Average Lifetime Cost per Child of Selected Birth Defects and Outcomes; CDC 2004 .....	15
Table 2: Estimates of Average Lifetime Cost per Child of Selected Birth Defects and Outcomes; CDC 1995 .....	15
Table 3: Response Options and Frequencies for Teratology Information Service Goals.....	36
Table 4: Percent of Time Spent Counseling on Different Topics.....	37
Table 5: Time Spent Offering Various Services.....	38
Table 6: Groups counseled by TIS.....	42
Table 7: Discrete Choice Experiments Evaluating Women’s Health Services .....	59
Table 8: Common Attributes in Discrete Choice Experiments of Women’s Health Services .....	62
Table 9: Focus Group Details .....	67
Table 10: Attribute Rating by Focus Group Participants.....	69
Table 11: Willingness-to-Pay Ranges from Focus Groups.....	69
Table 12: Literature Review of Willingness-to-Pay for Attributes of Women’s Health Services	70
Table 13: Attributes and Levels Used in the Pilot Survey .....	71
Table 14: Advantages of Offering Opt Out/None Option .....	74
Table 15: Results of Multinomial Logit Regression Analysis of Pilot Choice Data (n=21) .....	82
Table 16: Sample Question from Final Survey.....	84
Table 17: Properties, Advantages, and Disadvantages of Potential Discrete Choice Regression Models.....	89
Table 18: Recruitment of Participants .....	93
Table 19: Cost and Success of Recruitment Methods .....	94
Table 20: Demographic Characteristics of Survey Respondents (total n=175).....	95
Table 21: Responses to Health-related Questions .....	97
Table 22: Comparison of Online and Paper Respondents .....	97
Table 23: Level of Anxiety about Exposed Pregnancy .....	97
Table 24: Results of Main Effects Multinomial Logit Regression Model.....	99
Table 25: Regression Model Including Significant Interactions with Demographic Variables .	100
Table 26: Calculation of the Marginal Utility of Money .....	103
Table 27: Willingness-to-Pay Based on Interaction Model.....	103

Table 28: Model Fit Statistics .....	105
Table 29: Regression Model Stratified by Education .....	106
Table 30: Change in Cost Coefficient by Respondent Level of Anxiety about the Pregnancy Exposure .....	107
Table 31: Dominant Decision Makers .....	107
Table 32: Illogical Decision Makers .....	108
Table 33: Impact on Regression Model of Excluding Dominant and Illogical Decision Makers .....	109
Table 34: Demographic Characteristics of Illogical Decision Makers .....	109
Table 35: Demographic Characteristics of Cost Dominators .....	110
Table 36: Choice of Most Important Attribute Compared to Importance Scores .....	111
Table 37: Responses to Fixed Choice Task Comparing TIS and Family Doctor .....	112
Table 38: Comparison of Best and Worst Service Scenarios .....	112
Table 39: Responses to Question: “Check all information sources you would consult” .....	113
Table 40: Distribution of Number of Sources Picked .....	113
Table 41: Willingness-to-Pay for Service Attributes .....	129
Table 42: Levels and Willingness-to-Pay for TIS in First Approach .....	130
Table 43: Levels and Willingness-to-Pay for TIS in Second Approach .....	131
Table 44: Levels and Willingness-to-Pay for Family Doctor Visit .....	131
Table 45: Variables and Ranges Used in the Probabilistic Sensitivity Analysis .....	138
Table 46: Results of Probabilistic Sensitivity Analysis: Approach One, Productivity Costs Included .....	140
Table 47: Results of the Probabilistic Sensitivity Analysis for the Second Approach, Productivity Costs Included .....	145
Table 48: Results of Analysis from the Health Care System Perspective, First Approach .....	145
Table 49: Results of Sensitivity Analysis for Model Uncertainty from Health Care System Perspective .....	146
Table 50: Comparison of Aggregated Willingness-to-Pay Estimates to Ceiling Costs in Previous Discrete Choice Experiments .....	150

## List of Figures

Figure 1: Consequences of Investments in Child Health.....	20
Figure 2: Conceptual Framework: Health Consumer’s Decision Process.....	26
Figure 3: States and Provinces with TIS.....	35
Figure 4: Relative Utility Gains for Preferred Levels.....	101
Figure 5: Comparison of Importance Score with Response to Explicit Choice of Most Important Attribute .....	111
Figure 6: The Incremental Cost-Effectiveness Plane.....	141
Figure 7: Scatter Plot of Incremental Costs and Incremental Benefits Plotted in Cost-Benefit Plane.....	142
Figure 8: Histogram of Incremental Net Benefit .....	143
Figure 9: Sensitivity of Incremental Net Benefit to Input Variables .....	144

## List of Appendices

Appendix 1: Research Ethics Board Approval for Survey of Teratology Information Services

Appendix 2: Research Ethics Board Approval for Discrete Choice Survey

Appendix 3: List of Research Ethics Board Amendments

Appendix 4: Survey of Teratology Information Services (North American Version)

Appendix 5: Consent Form for Focus Groups

Appendix 6: Audio Consent Form for Focus Groups

Appendix 7: Focus Group Discussion Questions

Appendix 8: Focus Group Attribute Rating Form

Appendix 9: Newspaper Advertisement for Discrete Choice Survey

Appendix 10: Discrete Choice Survey Consent Letter

Appendix 11: Discrete Choice Survey (Version 1)

Appendix 12: Distributions for Incremental Benefits and Incremental Costs in the Cost-Benefit Analysis

## List of Abbreviations

CA – Conjoint Analysis  
CBA – Cost-Benefit Analysis  
CDC – Center for Disease Control  
CDR – Common Drug Review  
CEA – Cost-Effectiveness Analysis  
CI – Confidence Interval  
CUA – Cost-Utility Analysis  
CV – Contingent valuation  
DCE – Discrete Choice Experiment  
EHC – Emergency Hormonal Contraception  
ENTIS – European Network of Teratology Information Services  
FAS – Fetal Alcohol Syndrome  
FASD – Fetal Alcohol Spectrum Disorder  
FDA – Food and Drug Administration  
FTE – Full Time Equivalents  
GP – General Practitioner  
HBM – Health Belief Model  
HCP – Health Care Professional  
HCV – Hepatitis C Virus  
HIV – Human Immunodeficiency Virus  
HMO – Health Care Maintenance Organization  
HSC – Hospital for Sick Children  
IQWiQ – Institute for Quality and Efficiency in Health Care  
IVF – In Vitro Fertilization  
LBW – Low Birth Weight  
MD – Medical Doctor  
MNL – Multinomial Logit  
MRS – Marginal Rates of Substitution  
NICE – National Institute for Health and Clinical Excellence  
NIOSH - National Institute for Occupational Safety and Health

NTD – Neural Tube Defect  
NVP – Nausea and Vomiting of Pregnancy  
OECD – Organisation for Economic Co-operation and Development  
OMEP – Orthogonal Main Effects Plan  
OTIS – Organization of Teratology Information Specialists  
PSA – Probabilistic Sensitivity Analysis  
QALY – Quality Adjusted Life Years  
QoL – Quality of Life  
RP – Revealed Preference  
SD – Standard Deviation  
SE – Standard Error  
SSRI – Selective Serotonin Reuptake Inhibitor  
SP – Stated Preference  
TERIS – Teratogen Information System  
TIS – Teratology Information Services  
USD – United States Dollar  
VAS – Visual Analogue Scale  
WHO – World Health Organization  
WTP – Willingness-to-Pay

# 1 Chapter 1: Introduction

## 1.1 Overview

This chapter provides a broad introduction to the field of teratology, the role of Teratology Information Services (TIS) in providing teratology counseling, the need for an economic evaluation of TIS, and the methods that were used to conduct an economic evaluation of a TIS counseling encounter. The effectiveness of counseling by TIS in improving maternal and neonatal health outcomes will be reviewed, as well as previous evaluations of programs that promote health during pregnancy and telehealth in general. The need for an economic evaluation of TIS will be explained. A rationale will be provided for the selection of a cost-benefit evaluation method, with benefits measured using willingness-to-pay data derived from a discrete choice experiment. The hypothesis and research objectives will be described, and subsequent chapters introduced.

## 1.2 Teratology Information Services

Congenital malformations and other forms of adverse fetal outcomes are a public health concern and the focus of numerous initiatives in health care. Birth defects are the leading cause of infant mortality, and are responsible for one in every five infant deaths (infants being one year of age or younger) [1]. Furthermore, in 1992 birth defects were the second leading cause of death amongst children aged one to four years, and the third leading cause of death amongst children aged five to nine years [2]. Although it has been estimated that only about 1% of birth defects are attributable to medication use in pregnancy, 65% of birth defects have an unknown etiology and it is possible that a portion of these may be attributable to medication use [3]. It has been found that 86% of pregnant women are exposed to more than one medication [4]. An Italian study found that on average, pregnant women are exposed to 4.7 medications (including vitamins), and were most commonly exposed to analgesics, antiemetics and antacids [5]. Pregnant and lactating women, however, are routinely excluded from clinical research, and therefore there is a lack of data available to guide appropriate medication use. There is a clear need for experts to guide pregnant women in the appropriate use of medications.

Teratology Information Services (TIS) have emerged in response to this need for experts to help interpret complex and often deficient or conflicting data on teratological risks following

exposures during pregnancy. This need has emerged in the last century, particularly following the thalidomide disaster of the 1960s [6]. TIS are multi-disciplinary programs that provide information on drug safety, environmental exposures, genetics, disease in pregnancy, addiction in pregnancy, and nutritional supplementation. TIS focus on advising pregnant women, women planning pregnancy, breastfeeding women, and their families and health care providers (HCPs) on the reproductive safety or risk of prenatal and lactational exposures, mainly via telephone call centres. This includes providing information regarding medicinal drugs, drugs of abuse, chemicals, infections, and occupational and environmental agents. Additionally, these services counsel men who have been exposed to drugs and chemicals and have concerns about teratogenicity or mutagenicity [7]. Ideally, counseling would occur while a pregnancy is in the planning stage, however half of all pregnancies are unplanned [8], therefore counseling during pregnancy occurs.

Individual TIS were first formed in 1979 with collaborative organizations emerging shortly thereafter [6]. OTIS (the Organization of Teratology Information Specialists) and ENTIS (the European Network of Teratology Information Services) were both formed in 1990. The goals of OTIS were initially to enable TIS to provide the most current information to the public and health professionals, to provide and maintain databases to improve knowledge on environmental exposure risks, to decrease the number of preventable birth defects, to provide reassurance regarding exposures that are not known to be of risk, and to organize annual meetings for knowledge exchange [9]. In 2007 the OTIS Board of Directors updated their mission and goals, with a focus on education, research, and collaboration [10].

Individual TIS and OTIS have been successful in creating and maintaining teratology databases such as Reprotox [11] and TERIS (The Teratogen Information System) [12], and in creating collaborative research networks leading to scientific publications on a variety of pregnancy exposures [13-24]. In 2003, more than 100,000 telephone consults were performed by TIS in North America [25]. However, the number of TIS has fluctuated, largely due to losses in funding support from state and local governments. According to the OTIS Board of Directors, there were 29 TIS in North America in 2002, and by 2006 this number had dropped to 18. While several descriptive reports exist of the value TIS users place on the service, described by satisfaction surveys or individual statements [26, 27], the value of TIS has not yet been systematically evaluated. Resource allocation decision-making in health care is increasingly being informed by

economic evaluations of health care programs [28]. An economic evaluation of TIS is warranted in order to inform resource allocation decision-making.

### 1.3 Effectiveness of TIS in Improving Maternal and Neonatal Outcomes

The objective of the following section is to review the published evidence of the clinical effectiveness of TIS in improving maternal and neonatal health outcomes. The impact of TIS on several health outcomes will be examined, including the prevention of congenital malformations, unnecessary pregnancy terminations, and occupational risks [8]; the ability of TIS to support optimal nutritional supplementation [29] and optimal drug therapy during pregnancy [30] and breastfeeding [31]; to correct misperceptions of risk [32]; and to facilitate knowledge transfer and translation [33]. The potential for health care cost savings as a result of TIS activities will also be examined.

#### 1.3.1 Prevention of congenital malformations

The prevention of congenital malformations is a major objective of TIS. There are two dimensions to the prevention of birth defects: primary and secondary. Primary prevention describes the prevention of the birth defect before it develops, such as through health and educational interventions prior to conception and during pregnancy. Secondary prevention describes the prevention of the birth defect after exposure to the teratogen has occurred, such as through pregnancy interruption following prenatal diagnosis or surgical correction [34]. There are approximately 20 medications currently on the market that have been universally acknowledged to be teratogenic (such as isotretinoin, Angiotensin Converting Enzyme [ACE] inhibitors, and alcohol) [3]. By advising women who have been or may be exposed to human teratogens about their effects, TIS have been shown to secondarily prevent major malformations [8].

Motherisk is a TIS located in the Hospital for Sick Children (HSC) in Toronto, Canada [35]. In an early study, Motherisk was estimated to counsel 94 women in their clinic each year whose fetuses had been exposed to a teratogen [8]. Of these 94 women, 53 went on to either have a definitive antenatal test for malformations or to terminate pregnancy. Based on the known rates of drug-induced malformations in humans for the agents in question, it was estimated that five

major malformations would be secondarily prevented per year as a result of the TIS' clinic-based counseling [8]. It was found that virtually all patients exposed to systemic retinoids chose to terminate their pregnancy, and that virtually all those exposed to valproic acid or carbamazepine underwent tests to rule out neural tube defects (NTDs) [8]. This estimate did not include those women who had been counseled over the telephone, which represents the majority of the service's patients, and is therefore likely an underestimation of the effectiveness of TIS in the secondary prevention of malformations. By performing peri-conceptual counseling, TIS help to minimize or eliminate teratogenic exposures. The effectiveness of TIS in the primary prevention of malformations has not yet been fully quantified.

### 1.3.2 Prevention of unnecessary pregnancy termination

Numerous women are inappropriately advised, or may decide themselves, to terminate otherwise wanted pregnancies due to the perception of risk associated with apparently safe medications, such as acetaminophen, antibiotics, or antihistamines [36], and environmental exposures such as diagnostic radiation [37]. TIS probably prevent numerous such terminations and the consequent maternal stress, anxiety, post-abortion morbidity and costs to the health care system.

A study conducted at Motherisk assessed women's tendencies to terminate their pregnancies after receiving appropriate counseling at their clinic [37]. An analysis of all women who visited the clinic between September, 1986 and January, 1988 revealed that there were 123 clinic visitors in that time period who expressed a less than 50% tendency to continue their pregnancy prior to counseling; outcomes for 78 of these women were available at the time the study was published [37]. The tendency to continue pregnancy was measured by a 100-point, 10 centimetre visual analogue scale (VAS), where zero represented an absolute tendency to terminate pregnancy and 100 represented an absolute tendency to continue pregnancy; tendencies were measured before and after counseling. Sixty-one women (78%) significantly changed their tendency after their counseling experience, from a VAS score of  $34.3 \pm 2.5$  to  $84.5 \pm 3.3$  ( $P < 0.00001$ ). These 61 women subsequently had 57 normal, healthy infants and four miscarriages [37]. Of the 17 women (22%) whose tendencies to continue pregnancy were unchanged following counseling, all went on to terminate their pregnancy. Only two of the 17 women had been exposed to teratogenic drugs, while others identified reasons unrelated to their exposure as the leading reason for termination. This study demonstrates that an appropriate

counseling intervention in early pregnancy can prevent unnecessary terminations by correcting misinformation and decreasing risk perception.

These results were duplicated in a study by an Italian TIS, which found that a percentage of voluntary abortions were related to suspected teratogen exposure and that their TIS was effective in preventing voluntary abortions caused by fear of teratogenicity [38]. Furthermore, women who missed a counseling appointment with a TIS were less likely to be pregnant at 20 weeks gestation than women who attended the clinic [39].

Interestingly, the Italian study found that while four of 350 women who terminated a pregnancy reported exposure to a suspected teratogen as the reason for termination, only one woman had a confirmed exposure [38]. In a study of the safety of anti-histamines in pregnancy, pregnancy outcomes for 120 women exposed to either hydroxyzine or cetirizine during pregnancy were prospectively obtained. In this study, two women reported having therapeutic abortions based on fear of the effects of the drug exposure to the fetus [36]. It is possible that women who are conflicted in their decision to terminate may cite exposure to a teratogen as the reason for their decision. The extent to which this occurs is unknown.

Understandably, women may become very anxious following exposures during their pregnancies and may have unrealistically high perceptions of risks to their fetus. TIS provide counseling and information that will better inform women's decision-making processes, which has been demonstrated to reduce terminations of otherwise wanted pregnancies.

### **1.3.3 Support of optimal folate and vitamin supplementation to improve child health**

Many studies have demonstrated the benefits of vitamin and folate supplementation during pregnancy. It has been shown that peri-conceptual ingestion of folate reduces the incidence of NTDs, especially among high-risk women and women in their first pregnancy [40]. Women in high-risk categories for NTDs (including obese women, women with diabetes, and women with a family history of spina bifida) are recommended to supplement with 5 mg of folic acid daily [41, 42]. Awareness of the need for increased supplementation for these high-risk groups is low [43]. Women receiving a folic acid antagonist (such as valproic acid or carbamazepine) are also at an increased risk of having a baby with an NTD, and while high-dose supplementation with folate

(up to 5 mg/day) is currently recommended for these women, it has not yet been shown to reduce the incidence of NTDs in this group. Folate consumption to prevent NTDs is supported by the Center for Disease Control [44] and the Public Health Agency of Canada [45].

In addition to NTD prevention, folic acid supplementation has also been suggested to reduce the incidence of neuroblastoma, a childhood cancer [46], although confirmation of this effect is required. Supplementation with folate has not been implicated in the prevention of non-neural birth defects [47]; however, it is possible that supplementation with multi-vitamins may confer benefits. A recent meta-analysis has found that prenatal supplementation with multi-vitamins may reduce the risk for many types of birth defects, including cardiovascular defects, limb defects, cleft palate, oral cleft with and without cleft palate and urinary tract anomalies [46].

Unfortunately, many women do not supplement with vitamin and folate regimens, as they may be unaware of the health benefits for both themselves and their fetus, or they find that these regimens worsen their nausea and vomiting of pregnancy [48]. Improving vitamin supplementation of pregnant women can be achieved readily with relatively simple means. In one study, women who were provided with a brief counseling session regarding the benefits of folic acid, 30 free folic acid tablets and a reminder phone call about supplementing, had a significantly increased folic acid intake compared to a no-intervention control group [49]. The women who were most influenced by the intervention were black, had a lower income and were not planning pregnancies. The authors hypothesized that such simple counseling may decrease the incidence of NTDs by 11% [49].

Research has also shown that the advice of TIS to women planning pregnancy is effective in ensuring adequate folate supplementation during embryogenesis. A study by Motherisk showed that counseling women planning pregnancy about folate supplementation resulted in 71% of those women consuming folate, compared to only 17% who were not counseled [29]. While overall folate levels have improved since 1997, when fortification of flour with folate was first legislated, a relatively large proportion of women may still have sub-optimal folate levels, so there is still potential for NTDs to be prevented [50]. While many doctors now routinely recommend folate supplementation, awareness about the role of supplementation in reducing NTDs as well as adequate timing and dosing remains low [51]. TIS counseling improves folate

and vitamin supplementation in pregnancy, which measurably prevents NTDs and potentially birth defects and childhood diseases, as well as improves maternal health.

#### 1.3.4 Support of optimal drug therapy during pregnancy

For many women, drug therapy is required during pregnancy for chronic medical conditions such as depression, diabetes, hypertension, and asthma. Women are commonly advised to abruptly stop such therapy during pregnancy, or choose to do so themselves due to an unrealistic perception of risk to the fetus [30].

There is compelling evidence that leaving maternal conditions untreated during pregnancy may lead to *increased* fetal risks, including intrauterine growth restrictions and stillbirth. The continuation of therapy or properly tapering or switching to alternate therapies or doses may therefore be essential to the health of both mother and fetus. For example, asthma affects up to 8% of pregnant women [52]. Asthma requires adequate pharmacotherapy for proper management and has been found to worsen in pregnancy [53]. Untreated asthma has been found to increase risks for low birth weight [54] and prematurity [55].

Another common condition in pregnancy is depression. Prevalence estimates range from 7-15% [56]. Women have a twofold higher rate of depression than men, and are at an increased risk for depression onset in their childbearing years [57, 58]. Women who discontinue their anti-depressant medications have been found to be more likely to have major depressive relapses than women who continue their medications throughout pregnancy [59]. Untreated depression has numerous consequences: it has been shown to almost double a woman's risk of having a spontaneous abortion [60] and to increase the risk of low birth weight and pre-term delivery [61]. It has also been suggested to affect suicidality [62], risk of post-partum depression [62], and may lead to abuse of other drugs or substances such as alcohol [30].

TIS have been shown to support optimal drug therapy during pregnancy. A Motherisk study of women who had called the service and who had stopped taking their prescribed anti-depressants or benzodiazepines after determining they were pregnant were interviewed following reassuring counseling regarding the safety and risks associated with their medications [30]. After counseling, 22 of 36 (61.1%) women resumed taking their medication (four had found that they no longer needed it) [30]. This study demonstrates the dramatic consequences to abrupt

discontinuation of anti-depressant medication, as almost one third of the women (11/36) reported suicidal ideation and four required hospitalization after discontinuing their medication [30].

In addition to the long-term prescription medications discussed above, many women will avoid taking short-term prescription and non-prescription medications such as acetaminophen, antibiotics and anti-histamines during pregnancy due to fears and misconceptions about their safety. Avoiding these medications may lead to losses in productivity as well as have a negative impact on overall maternal health. The use of medications is becoming increasingly common in Western societies. A survey of 2,590 American adults found that 81% had taken a medication in the preceding week, with hypertension and headache being the most common indication for medication use [63]. It has also been found that women use a greater number of prescription drugs than men, and that these gender differences are most apparent during a woman's child-bearing years [64]. As medication use is common amongst women of child-bearing age, services that provide evidence regarding the effects of medications during pregnancy are of great importance to women's health.

Unfortunately, risk perception is high not only among women, but among their care-givers as well. Empowering HCPs to treat pregnant women appropriately is a major objective of TIS. One study found that a convenience sample of Canadian pharmacists, physicians, nurses, and hospital workers rated a sample of four medications as unsafe in pregnancy despite a scientifically reassuring text on the medical label [65]. HCPs may lack evidence-based information on medication safety in pregnancy, and existing data may be difficult to interpret, further emphasizing the need for public access to information services. Appropriate counseling provides women and their caregivers with the information necessary to make informed decisions regarding medication use in pregnancy, weighing risks and benefits.

### 1.3.5 Prevention of Occupational Risks

Women of reproductive age currently comprise 46% of the Canadian workforce [66]. There is a potential risk of exposure to toxic chemicals in the workplace for many women. For example, pregnant women exposed to organic solvents are at an increased risk for malformations and spontaneous abortions compared to women not exposed to solvents [67]. Organic solvents are one of the most widely used groups of chemicals in the workplace. The National Institute for Occupational Safety and Health (NIOSH) has identified 335 different occupations which have

the potential to expose workers to solvents. NIOSH estimates that in the United States, three million women and six million men are occupationally exposed to solvents [68]. TIS advise women on the safety or risk of workplace exposures, enabling them to distinguish between safe and unsafe practices. This information may prevent a loss of productivity for the woman and/or prevent adverse fetal outcomes.

### 1.3.6 Support of Breastfeeding

Avoiding breastfeeding due to misconceptions about the risk of medicinal drugs to the baby may adversely affect the infant, as they will lose the demonstrated health and psychological benefits it provides [69]. The World Health Organization (WHO) and UNICEF recommend that women breastfeed exclusively for the first six months of life, and use it as a supplemental source of nutrition to 24 months and beyond if desired [70]. Breastfeeding has also been shown to be cost-effective, providing savings to both the health care system and breastfeeding mothers [71]. Many women are discouraged from breastfeeding when they need medications, or they themselves may decide not to breastfeed due to their misperceptions of risk [31]. Most medications are safe during lactation [72]. TIS educate women about exposure risks, and this may empower them to continue breastfeeding and thereby achieve the superior health outcomes associated with this practice.

### 1.3.7 Knowledge Transfer and Translation

TIS are utilized by HCPs as well as patients. TIS perform and report evidence-based studies to clinicians, who may apply this information to their practice. Teratology specialists based at TIS publish numerous scientific papers and present research at local and international forums. TIS are excellent research resources as they are well positioned to gather information from their callers and perform safety surveillance of medications [21, 33, 73]. The value of this information to clinicians is high and will benefit future patients.

As previously mentioned, lack of understanding regarding teratogenic risks is common, even amongst HCPs. As drug use in pregnant women is rarely studied, there is often little data available to inform prescription practices [74]. Traditional classification systems of drugs according to risk category may be confusing to women and their HCPs [75]. Current labeling systems leave HCPs with little guidance for prescribing medications during pregnancy [76].

Medication labels often provide conflicting advice compared to drug information centres, leading to diversity in clinical practice and confusion amongst patients and caregivers [77]. Conversely, potentially teratogenic medications are prescribed to millions of women of childbearing age each year [78]. A retrospective registry-based study in Finland found that 3.4% of a cohort of pregnant women purchased at least one drug clearly labeled as harmful to the fetus during pregnancy [79]. The Food and Drug Administration (FDA) Pregnancy Labeling Taskforce has recommended replacing current letter categories (A, B, C, D, X) with a narrative text that includes clinical management advice [80]. Current deficiencies have been acknowledged and major reform of medication labels is underway, with a proposed plan to replace the five letter codes with three text sections: risk summary, clinical considerations, and data [81].

Many deficiencies in the care of women requiring medications during pregnancy have been identified. A survey of 70 women with bipolar disorder demonstrated that many HCPs lack the skills necessary to advise women who require medications during pregnancy [82]. Forty-five percent of the women in the study had been advised by health care professionals to avoid pregnancy [82]. After appropriate counseling and an assessment of the risks and benefits of individual medications conducted by a TIS, 63% of women in this survey went on to pursue a pregnancy [82]. Another example of the important role of TIS in addressing deficits in standard care was found in a survey of pregnant women calling TIS who were taking isotretinoin, a known teratogen. This study found that almost one-quarter of these women did not receive pregnancy-prevention counseling at the time of their prescription [22]. Another study found that in 53 isotretinoin-exposed pregnancies, only 41% of the women reported using a birth control method [83]. Furthermore, as previously discussed, women may be wrongfully advised to terminate pregnancies following non-teratogenic exposures [84].

The extent to which physicians rely on TIS support was demonstrated in a survey of physicians who had called Motherisk [85]. Surveys were sent to 200 doctors who had used the Motherisk program in the previous month; 118 surveys were returned [85]. It was found that 91% of physicians reported repeating the information they had received from the TIS to their patients verbatim, even though 48% researched their questions themselves in advance of the call [85]. Teratology specialists are also needed to assist in the diagnosis of rare disorders with which primary care-givers may not be familiar. A survey of Canadian family physicians found that their confidence in diagnosing Fetal Alcohol Syndrome (FAS) was low, and none of the physicians

were aware of current screening methods to gauge alcohol use in pregnant women [86]. A survey of general practitioners (GPs) in Norway found they ranked the quality of information provided by their local TIS as very high [87].

### 1.3.8 Reducing Anxiety and Correcting Risk Misperceptions

Since the thalidomide disaster in the 1960s, fears about the teratogenic risk of prenatal exposures have persisted. TIS receive numerous calls from women and their partners who are extremely concerned about innocuous exposures. Media and other sources may provide misleading statistics and information, provoking fear and anxiety. For example, in 2004, Health Canada and the FDA released advisories on the risks associated with the use of anti-depressants in pregnancy. While neither of the advisories suggested that women cease their medication use, 49 women called Motherisk after hearing of the advisories in the media in the week following the advisory [88]. All of the callers reported that the media coverage caused them a great deal of anxiety; five women had discontinued their antidepressants and six were considering discontinuation, but decided to continue following reassurance from Motherisk [88]. This report on the Motherisk experience following the advisories demonstrates the impact of the media on women's perceptions and activities, and also that TIS are important resources in correcting misinformation. An earlier study of a Quebec pregnancy healthline, Info-Grossesse, provides further evidence of the success of telephone counseling in reducing teratogen related fears. A satisfaction questionnaire found that for about three quarters of the respondents the service had decreased their concerns and answered all their questions [89]. While the program no longer operates in this form, it used to receive approximately 80 calls per month [89].

Numerous studies have demonstrated that appropriate counseling can reduce risk perception [8, 90-92]. The baseline risk of birth defects in the general population is 1-3%. In one study, women exposed to non-teratogenic agents assigned themselves a mean risk of  $24\% \pm 2.8\%$  for major malformation before counseling. The baseline risk for malformations in the general population is only one to three percent [8]. To put this perception of risk into context, the risk for malformations associated with isotretinoin use is approximately 21% [90]. Sadly, women exposed to non-teratogenic agents believed they had the same risk for malformations as the actual risk associated with isotretinoin, one of the most severe known teratogens. The risk perception these women assigned themselves was reduced to  $14.5\% \pm 3\%$  after counseling [8].

Women exposed to ionizing radiation during pregnancy assigned themselves a risk for malformations of  $25.5\% \pm 4.3\%$  prior to counseling. Following counseling, their risk perception fell to the same level as a control group [91]. Similar results were found in a study examining the risk perception of cocaine: after counseling, women's risk perception decreased significantly from  $37.5\% \pm 20.5\%$  to  $17.6\% \pm 14.2\%$  [92].

The perception of teratogenic risk is high, even for safe exposures, and is difficult to change even with sound evidence. Inexperienced readers will often overestimate an exposure risk based on a single case report or study [93]. One study found that the risk perception of women and health professionals for a medication (which had been shown to be safe to the fetus) used in the treatment of nausea and vomiting of pregnancy (NVP) was not altered by a label containing reassuring scientific evidence of its safety [65]. Another study found that 52% of pregnant women who chose to not use a cream rinse for head lice treatment did so because they did not feel the information provided to them was adequately reassuring, even though the use of this product has not been associated with an increased risk for adverse pregnancy outcomes [94].

Pregnant and lactating women will have unique concerns during public health emergencies, such as disease outbreaks or natural disasters. TIS are able to respond quickly to such events, and may be particularly useful in such situations when people are displaced from their usual HCPs. A report on the OTIS response to Hurricane Katrina in 2005 described the actions of TIS, which included providing online statements regarding Hurricane-related exposures such as mould, contaminated water, and stress [95]. The OTIS toll free national line also added an option for callers with specific hurricane-related concerns [95].

Reducing risk perception through appropriate counseling may have numerous benefits that are difficult to quantify, such as alleviation of anxiety and improvement in quality of life. The challenges in measuring such effects however, should not preclude them from being included in an analysis of the clinical effectiveness of TIS.

### 1.3.9 Conclusions from Literature Review of TIS Effectiveness

This literature review has demonstrated that TIS are effective in improving maternal and neonatal health outcomes. The provision of information has potentially enormous public health benefits, and TIS have already demonstrated clinical effectiveness and high levels of satisfaction

amongst users. The value of health information has been demonstrated by recent campaigns to educate the public regarding the negative effects of cigarette smoking [96]. Information campaigns on this topic have helped to reduce the number of U.S. smokers from an estimated 70 million in 1964 to 45.8 million in 2005 [96]. Public health efforts to provide information about the safety and risks of exposures in pregnancy and lactation through TIS may lead to similar future success stories. The evaluations of pregnancy health information programs to date, however, have mainly been limited to observational studies and satisfaction surveys. More rigorous research is needed to determine effectiveness and value for money.

## 1.4 Introduction to Economic Evaluations and Utility Measurement in Health Economics

Economic evaluations of health care programs endeavor to compare the costs and consequences of a given program or intervention. There are three basic types of economic evaluations in health care, and they differ in how they measure program consequences. Cost-effectiveness analyses (CEA) measure program consequences in natural health units, for example heart attacks avoided or life years gained. In a cost-utility analysis (CUA), program consequences are measured in quality-adjusted life years (QALYs). QALYs are calculated by multiplying utilities by life expectancy. Utilities refer to preferences for a health state and are most often measured on a scale from 0 (representing death) to 1 (representing full health) [97]. There are several methods of measuring utilities, and the type of measurement used may depend on the research question. Questions regarding preferences may be asked when outcomes are certain or uncertain, and the respondent may be asked to rank or rate the choices provided [97]. Utilities may be obtained directly, by asking respondents to trade off or gamble future life for a reduced time in perfect health, or indirectly, such as with standardized questionnaires [98]. In a cost-benefit analysis (CBA), program consequences are measured in monetary terms, and this method will be described further in section 1.10.

## 1.5 Economic Evaluations of Programs Promoting Health and Providing Counseling in Pregnancy

While large investments in neonatal care are common, little emphasis has been placed upon the value of providing information that may prevent, and/or provide reassurance regarding, adverse neonatal outcomes. OECD countries (Organisation for Economic Co-operation and

Development, comprised of pluralist democracies with market economies) have typically under-invested in population-wide prevention and public health programs. On average, only 3% of all OECD health expenditures are directed towards prevention and public health, while the bulk of health care spending is focused on “sick care” [99].

Economic evaluations of health promotion and counseling programs are limited. WHO defines health promotion as “the process of enabling people to increase control over, and to improve, their health.” [100] A recent census of economic evaluations in health promotion found that the costs and effectiveness of interventions that address the social and economic determinants of health and the promotion of mental health have been rarely reported [101]. Another census of a longer time period (1976-1997) found only six cost-utility analyses of clinical preventive services categorized as “counseling” [102]. It has been generally argued that investment in child health is a sound economic decision as health in infancy and childhood sets the stage for long-term adult health and productivity [103, 104]. A review of the existing economic literature relating to pregnancy interventions will be provided in this section.

### 1.5.1 Costs of Birth Defects and Birth Defect Prevention

Costs of specific birth defects have been estimated. Economic evaluations of birth defect prevention on a population level via NTD prevention with improved folic acid levels have been conducted and are summarized in section 1.5.3. It is very difficult, however, to conduct economic evaluations of programs that aim to prevent birth defects on a patient level. Previous economic evaluations that have examined interventions in diabetic women (who are at a higher risk of having babies with malformation) have generally found that such interventions are cost-saving, mainly by reducing hospitalizations and hospital lengths of stay; prevention of birth defects was not measured [105-107]. There is preliminary evidence that the activities of TIS result in health care cost savings [8], which is intuitive given the high costs of even one malformation. The life-long costs of major malformations are high; some known costs of illness are presented in Table 1 and Table 2.

**Table 1: Estimates of Average Lifetime Cost per Child of Selected Birth Defects and Outcomes; CDC 2004**

<b>Malformation</b>	<b>Lifetime cost (2003 USD)</b>	<b>Reference</b>
Mental Retardation	\$1,123,876	CDC [108]
Cerebral Palsy	\$937,581	
Hearing Loss	\$424,507	
Vision Impairment	\$525,290	

**Table 2: Estimates of Average Lifetime Cost per Child of Selected Birth Defects and Outcomes; CDC 1995**

<b>Malformation</b>	<b>Lifetime cost (2004 USD)</b>	<b>Reference</b>
Spina Bifida	\$365,736	CDC [109]
Truncus arteriosus	\$628,220	
Transposition of the great vessels	\$332,148	
Tetralogy of fallot	\$325,928	
Tracheoesophageal fistula	\$180,380	
Cleft lip/palate	\$125,644	
Cardiovascular truncus arteriosus	\$628,220	
Colon, rectal, or anal atresia	\$153,012	
Reduction defect – upper limbs	\$123,156	
Reduction defect – lower limbs	\$247,556	
Gastroschisis	\$135,596	
Diaphragmatic hernia	\$311,000	
Down’s Syndrome	\$561,044	

These cost estimates were generated slightly differently. A discount rate of 3% was used in Table 1 [108], and 5% was used in Table 2 [109]. These costs include both direct (medical and non-medical such as special education and home services) and indirect costs (loss of productivity) [109]. Costs were inflated to 2004 values using the Canadian Consumer Price Index (CPI) as the historical U.S. CPI did not go back further than the year 2000 [110].

Many birth defects are associated with developmental disorders [111], therefore prevention may also result in cost savings for education programs. In addition to the health and education costs, a child with a birth defect will have an enormous impact on the family, and estimates of the costs of caregiver time for affected children are limited. The costs of caregiver time have only been estimated for caregivers of children with Down’s Syndrome and NTDs [112]. It is assumed that the time spent caring for a child with a birth defect would be greater than that of an unaffected

child, thereby reducing the time available to the caregiver for labour and other pursuits. These costs need to be included if the perspective of analysis is societal [113].

An indirect example of the potential cost savings associated with birth defect prevention was given by a U.S. study that examined the fiscal impact of a ban on second trimester abortions for prenatally diagnosed malformations. Health care costs for performing the abortions were compared with the lifetime health care costs of various birth defects [114]. Looking at their retrospective database of all the prenatally diagnosed malformations in the previous eight year period, the study found that the estimated lifetime cost for an average cohort year of a legislative ban on elective terminations for prenatally diagnosed abnormalities would be at least \$8.5 million for patients treated at one University-based hospital [114]. Costs of abnormalities were estimated using the lifetime costs of birth defects study previously cited [115]. Extrapolated to that hospital's state and country, a similar ban on second trimester elective terminations would have a net cost of \$74 million in Michigan and \$2 billion annually in the U.S. [114]. While politically sensitive, this study suggests the health care cost savings associated with avoiding birth defects are high.

#### 1.5.1.1 Costs of Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorder

Costs have been estimated for Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorder (FASD). FASD provides a good example of some of the difficulties in estimating societal costs of disorders as multiple systems are affected, including health, justice, housing and welfare. A 2004 review of previous cost studies found that estimates varied greatly because of varying prevalence estimates and different practices regarding costs for housing and productivity; the cost estimate cited by this review as one of the more robust was US\$2million per case (2002 US dollars) [116]. A recent Canadian study that included health care costs as well as out-of-pocket and productivity costs estimated that total annual costs associated with FASD per child were \$14,342 (2003 Canadian dollars) [117]. Another study estimated that the mean annual cost of health care for children from birth to 21 years of age with FAS was US\$2,342 per capita more than the annual average cost of care for children in North Dakota who do not have FAS [118]. A recent decision analytic model comparing the cost-effectiveness of universal or targeted screening programs for fetal alcohol exposure found that both models represented good value for money depending on what society would be willing to pay to improve child health

[119]. TIS provide information regarding alcohol and illicit drug exposures, but may also provide an important anonymous first step for pregnant addicts to access the health care system.

### 1.5.2 Prevention of Low Birth Weight

The causes of LBW are multifactorial, and are influenced by socio-economic, biological, and environmental inputs [120]. Prevention of LBW and prematurity is therefore very difficult. It has been noted that among wellness programs, perhaps the most dramatic cost saving opportunities exist in controlling the costs of premature and low birth weight (LBW) babies [121]. The costs of LBW have been estimated as high. One study found LBW accounting for 10% of all health care costs for children [122]. Another study found that 47% of the cost of all infant hospitalizations were related to LBW [123]. LBW costs can be related to the extra medical care and increased periods of hospitalization required for fragile babies, and can also include costs related to special education, early intervention, support services, and lost parental productivity [122]. One study found that the average total health care cost (including initial hospital costs and post-discharge health care visits) for the first two years of life for an extremely LBW infant (<1000g) was €104,635 and only €3,135 for normal weight infants [124].

While smoking cessation is not typically a subject on which TIS provide counsel, economic evaluations of smoking cessation programs in pregnancy demonstrate the cost savings that are possible through preventing one case of LBW, which TIS may achieve through alternate means. It has been estimated in a California cohort that an annual drop of 3-4 percent in smoking prevalence in pregnant women would prevent 1,300 LBW live births, leading to a potential direct health care cost savings of US \$21 million annually. This estimate did not include maternal health care costs [125]. A Dutch study estimated that if 200,000 additional women participated in pre-conceptional counseling on smoking cessation, 98 LBW infants, 10 very-low-birth-weight infants and 7 perinatal deaths could be avoided [126]. The authors suggested that the potential of pre-conception counseling to prevent significant lifetime costs for affected children would likely result in a favorable cost-savings balance.

Smoking cessation programs that provide health education have been found to be favourably cost-effective in the context of pregnancy. An economic evaluation of a health education program for pregnant smokers found that providing them with information about the effects of smoking and quitting resulted in a higher quit rate and a subsequent cost reduction in direct and

indirect health care costs due to fewer low weight births [127]. This study concluded that health education programs can be cost-beneficial. While this conclusion was within the context of education regarding smoking, it is possible that health education regarding other pregnancy exposures may have similar results.

A prenatal telephone counseling program has been evaluated to determine its cost-effectiveness in preventing LBW. African-American women who were attending a prenatal clinic and who were at risk for having pre-term or LBW babies were randomized to receive either the intervention (a telephone call from a registered nurse once or twice a week from the 24<sup>th</sup> to 37<sup>th</sup> week of gestation) or standard care. A reduction in the incidence of pre-term birth and LBW was found in the intervention group [128]. The cost of the intervention was found to be \$117 per patient. Based on the known costs of LBW, it was found that this program saved \$277 in direct health care costs per participant greater than 19 years of age. The costs of the program exceeded the cost savings in the group of women who were less than 18 years of age [128]. This was likely an underestimation of the cost savings associated with the program as only the direct short-term health care costs associated with LBW were included. Another telephone counseling program aimed at assisting low income pregnant women in quitting smoking has also been found to be cost-effective. [129]. Other studies, however, have not demonstrated benefits in all user groups [130]. Collectively, these studies demonstrate that simple preventative counseling programs that reduce the incidence of LBW may result in cost savings to the health care system.

### 1.5.3 Improving Folic Acid Levels

Given the many benefits of improving folate intake, it is not surprising that it has been shown to be cost-effective or cost-saving in several studies, with results varying depending upon what assumptions have been made and parameters used in the economic model [131]. One study estimated that if 200,000 women received pre-conceptional counseling regarding the benefits of folic acid, 22 NTDs may be avoided, based on an uptake rate of 50% [126]. Economic evaluations of fortification of the flour supply with folic acid have been favourable in many countries, demonstrating potential savings of millions of dollars due to the avoidance of costly NTDs [132-137]. A targeted NTD prevention program aimed at women with previous NTD-affected pregnancies has been found to have similar cost per QALY gained compared to other preventive services [113]. These studies were likely underestimates of the true cost savings

associated with folic acid supplementation as they did not address its role in preventing cancers [131]. Simple interventions that improve folic acid levels in women of childbearing age have great cost saving potential.

#### 1.5.4 Economic Evaluations of Other Pregnancy Outcomes

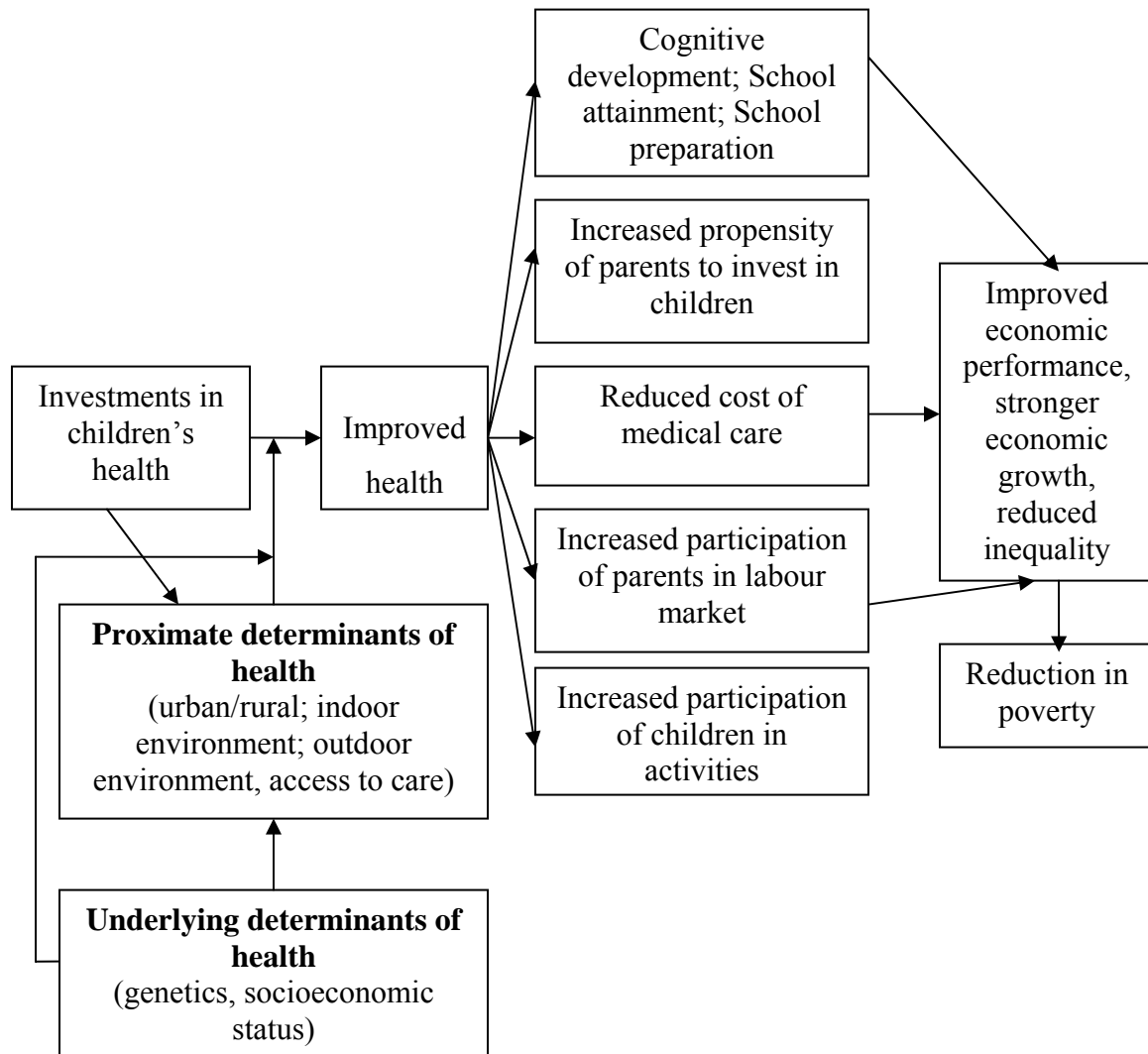
Costs have been estimated for several other health outcomes upon which TIS may have an impact. It has been determined that the cost of severe nausea and vomiting of pregnancy costs CDN\$610 (2002 dollars) per woman week [138]. An economic evaluation of prevention programs against congenital toxoplasmosis has been conducted [139]. If a pregnant woman is infected by the parasite *Toxoplasma gondii*, there is a 40-50% chance that the parasite will cross the placental barrier, which may damage the fetus' developing brain and eyes [139]. Treatment in pregnancy can reduce rates of transmission, therefore primary prevention and identification programs for pregnant woman are very important. An evaluation of two programs to prevent congenital toxoplasmosis, one consisting of health education of pregnant women on how to avoid infection, and one consisting of serological surveillance of pregnant women, found that while both were of an economic benefit to society, the cost of health education was less than serological screening [139]. Infants who were breastfed longer were found to have fewer hospitalizations and decreased health care costs in an Italian study [140].

While improving health during pregnancy and lactation can have an impact on a wide variety of maternal and child health outcomes, it is this variety that makes selecting an appropriate health outcome measure for economic evaluations of health education and promotion programs such as TIS difficult.

#### 1.5.5 Economic Consequences of Investment in Child Health

Investing in child health has the potential to provide numerous downstream consequences. Indeed, investment in neonatal and child health has the potential for greater lifetime returns on investment than any health investment [141]. A description of the potential consequences of investment in child health is provided in the diagram below.

**Figure 1: Consequences of Investments in Child Health**



**Consequences of Investments in Child Health:** Adapted from Belli C, Bustreo F, Preker A. Investing in children's health: what are the economic benefits? *Bull World Health Org.* 2005; 83: 777-784.

This diagram is useful to illustrating the numerous consequences of improved child health. In economic evaluations of child health interventions, gaining a true societal costing perspective through the measurement of productivity costs and costs to the education and justice systems can be difficult. Most economic evaluations also discount future benefits at a rate of 3-5%, which means that after approximately 30 years benefits become irrelevant; this undervalues lifetime health gains for children.

## 1.6 Health Care Cost Savings Associated with TIS

It is possible that TIS provide health care cost savings not only by improving maternal and child health outcomes but by alleviating pressure on other HCPs and services. There are case reports of women with extreme anxiety related to their pregnancies who repeatedly contact members of their health care team with teratological inquiries [142]. TIS have been able to successfully counsel and manage these women who worry excessively during pregnancy [142]. Information provided by TIS may also provide reassurance to women with perceived teratogenic exposures who would have otherwise sought expensive superfluous diagnostic tests, such as ultrasound or amniocentesis. This effect was demonstrated in a recent study that surveyed 420 callers to the Utah Pregnancy Risk Line [143]. Callers were asked before and after receiving counseling if they were likely to visit a prenatal provider to get information, and if they were likely to request testing for themselves or the baby because of their exposure. The study found that the likelihood of women wanting to visit a prenatal provider changed after counseling, such that 357 office visits and 149 ultrasounds may be avoided each year, resulting in a total potential cost savings of US \$54,264 [143]. It will be important to capture these potential cost saving activities in future studies. To date, an economic evaluation of TIS that weighs the costs of the program against potential health benefits has not been conducted. Additional rigorous research is needed to further demonstrate the effectiveness of the TIS model as a public health intervention.

## 1.7 Literature Review of Telephone-based Health Care

Telemedicine and telehealth programs have great potential for facilitating networking between colleagues, information exchange, and shared decision-making. Despite this potential, there have not been large investments in telemedicine and telehealth programs, which may be due to the lack of sufficient evidence of either their clinical or cost-effectiveness [144]. Telemedicine refers to the delivery of medicine over a distance, and generally involves the use of communications technology such as video conferencing or robotics, while telehealth refers more specifically to the provision of information, counseling, and advice via telephone. Evaluations of telemedicine and telehealth programs have been hindered by a lack of a comprehensive research strategy regarding accessibility, cost, and quality [144]. A qualitative study of six telehealth projects in the UK found that the evaluation of telehealth interventions is highly complex, and this complexity may be underestimated in the design of evaluation studies [145].

The clinical effectiveness of telehealth or telemedicine programs has been evaluated in contexts outside of teratology. The following studies were detected in a search of the PubMed database using the search terms “telehealth” and “effectiveness”. A systematic review for the Cochrane Collaboration found that telephone consultations decreased the number of doctor’s office contacts and out-of-hour visits to GPs [146]. A study conducted by an American health insurance agency found that providing telephonic nursing case management to pregnant women decreased by 2.5-fold the number of NICU admissions and maternal high risk conditions [147]. The women and children who received telephonic counseling also had lower health insurance costs [147]. Another study found that telephone counseling supported diet improvement efforts by increasing fruit, vegetable, and fibre intake and decreasing fat intake [148].

Telephone information services are also used by HCPs. Doctorline is a medical information service that developed from the need to continually update physicians on complex information. An evaluation found that the most common types of inquiries to Doctorline were from GPs regarding pharmacology [149]. This is not surprising given that the field of pharmacology is constantly evolving. Approximately half of calls to TIS are from HCPs [25].

The cost saving potential of telemedicine and telehealth has been suggested by previous research. It makes intuitive sense that advice provided via telephone may be less costly than in-person visits, both to the patient and the health care system. This has been documented in several studies. A survey of almost 5,000 Quebec telehealth line users found that approximately one third of callers would have otherwise visited a GP if the service were not available [150]. Further, 80% of respondents considered that they had saved an average of five hours of time and three hours of child care costs, 60% avoided transportation costs and 25% avoided losing time away from work [150]. In a similar study, 60% of callers to a rheumatoid arthritis nursing line reported they would have visited their doctor if a telephone nursing line had not been available [151]. An evaluation of a pediatric school-based telehealth program found that by avoiding lost productivity and travel, savings to families from using the telehealth service rather than a doctor ranged from USD \$101-\$224 per family per encounter [152].

Of course, it is important that the level of care provided by telephone not be less than alternatives. Reports of patient satisfaction and adherence with telehealth services and recommendations have been favourable. A survey of users of Quebec’s telehealth program found

that most were highly satisfied, had followed the advice given, and would call again [150]. These users also reported gaining a positive feeling of personal autonomy and self-reliance [150]. Another study found that users of a nursing triage telephone line reported rates of adherence to recommendations between 66-79%, depending on the nature of the advice [153]. Not surprisingly, higher adherence was found for the recommendation to visit an emergency department than the recommendation to visit a GP [153]. Interestingly, one study found that users of an information website on cancer therapy were more likely to request factual information and less likely to request information on sensitive topics than users of a telephone service on the same topic [154]. This finding was opposite to what the authors had hypothesized, and suggests that there is an important human dimension to telehealth that may not be present when information is provided over the internet. Similarly, there may be a difference in discussing medical information face-to-face rather than on the telephone, which has not yet been assessed. As well, studies of satisfaction are problematic as most satisfaction questionnaires obtain positive results, and individual definitions of satisfaction may vary [155].

## 1.8 Challenges in Performing an Economic Evaluation of TIS

Challenges will exist in the economic evaluation of any telemedicine or telehealth program. These have been outlined by McIntosh and Cairns [156]. The particular challenges they identified that apply to TIS include establishing an observable and empirical link between telehealth and improved patient outcome; inappropriateness of the conventional techniques of economic evaluation; and valuation of benefits, including non-health benefits, such as improvements in the process of care [156]. These challenges and others will be further described.

### 1.8.1 Selection Bias of TIS clients

TIS clients are self-selected from the general population, and have therefore identified themselves as being motivated to engage in healthy behaviours. It is likely that TIS clients may have a higher level of education and socio-economic status than the general population [157]. According to the Grossman model of the demand for health capital, individuals with more years of completed schooling have a longer life expectancy than other individuals [158]. This is thought to be due to the ability of people of higher education to be more efficient producers of health by engaging in healthy activities and lifestyle choices. People of higher education levels are thought to get a higher rate of return, or marginal productivity, from their health investments

as they are better able to utilize health information. It has been previously shown that while a telephone-based intervention program for women at risk of having babies of LBW was effective in preventing LBW for older women, similar benefits were not found in women in the program who were less than 18 years of age [128]. If it is determined that TIS clients have improved health outcomes, this effect may in fact be due to their higher education and socio-economic status and subsequent tendency towards greater health, rather than to the information provided.

### 1.8.2 Value of Information

It is very challenging to measure the value and impact of information. A study of women who called a TIS regarding the safety of anti-depressants in pregnancy found that some of the main determinants of their decision-making process was the information received prior to calling the TIS, the advice of family and friends, and the internet [159]. Clearly, decisions made by women following receiving information from a TIS will not be due to that information alone but will be part of a complex process with multiple influences and factors. The value of information provided by a TIS may therefore vary greatly between individuals.

### 1.8.3 Selection of a Comparator Program

While classic CEAs are comparisons between an intervention and a comparator, the selection of the comparator is difficult in performing an economic evaluation of TIS. Women who do not contact TIS may receive information from a myriad of alternative sources or programs. Potential comparator programs and information sources may include regular prenatal care, poison centres, pharmaceutical company registries, genetic counseling, media sources, public health sources, and any combination of these.

### 1.8.4 Measurement of TIS Outcomes

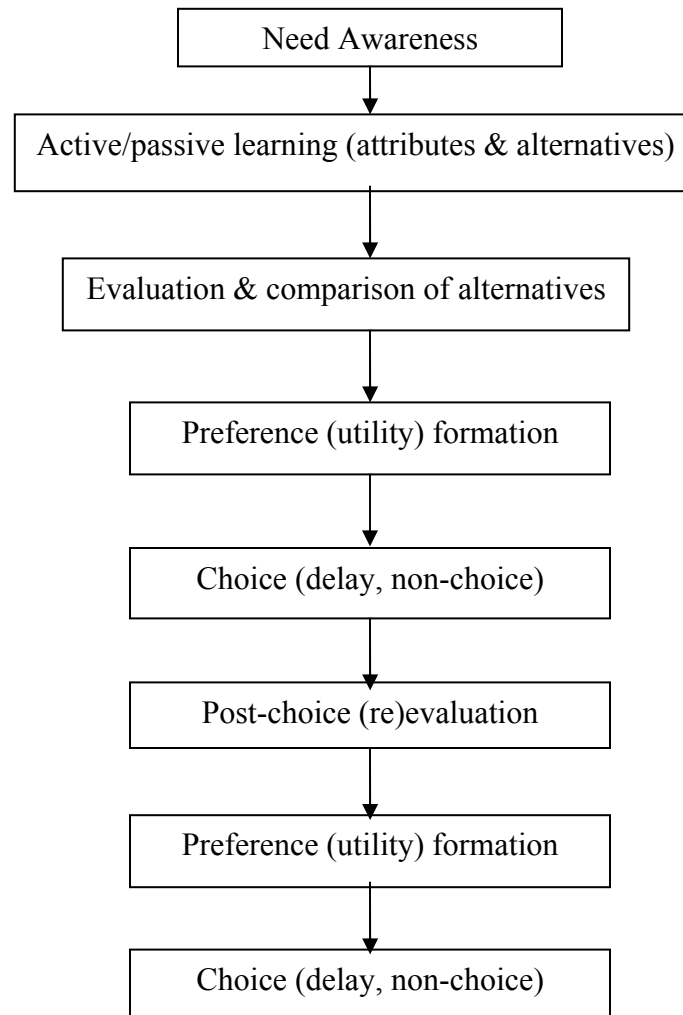
While some health outcomes associated with TIS are readily quantifiable, such as frequency of birth defects, there are several outcomes associated with TIS that are more difficult to measure, and to cost. There are also unique issues in assigning utility to fetuses; it has been shown choosing when to begin “counting” QALYs can change cost-effectiveness estimates for evaluations undertaken in the context of pregnancy [113, 160]. As previously described, TIS have been shown to greatly reduce anxiety and risk perception. Measuring the impact of the reduction in risk perception on health is challenging. The quantification of non-health benefits

associated with health care interventions has been termed “process utility,” and the correct methods of measuring the value of these benefits has been debated [161]. Willingness-to-pay (WTP) is one possible method of measuring the value of knowledge and reassurance. The value of such non-health features are not readily quantifiable when QALYs are measured [162]. It is also possible that these effects have an impact upon mental health such that they may be measured by a quality of life (QoL) index. The challenges in measuring such effects, however, should not preclude them from being included in an economic evaluation of TIS.

## 1.9 Introduction to Conjoint Analysis and Discrete Choice Experiments

Conjoint analysis (CA) is a survey method based on the theory that any good or service can be described by its characteristics, and that it is the characteristics that are valued by the individual rather than the good itself [163]. Therefore, the value placed on the good or service depends on the value the individual places on its characteristics [97, 164]. CA refers to the analysis of joint effects of attributes in determining choice. In a typical CA study, a respondent is presented with hypothetical scenarios that are described by a set of component outcomes or processes (characteristics or attributes). Attributes are given different levels, dictated by what has been identified as important in the provision of the good or service (for example, in a survey regarding a medical procedure, an attribute may be pain experienced, with levels of mild, moderate, or severe). Respondents are asked about their preference for different scenarios. Preferences can be measured by ranking, rating, or making discrete (binary) choices. Discrete choice experiments (DCEs) are a specific type of conjoint analysis study where preferences are measured through choice rather than ranking or rating. The preferences for each attribute can then be determined in a regression analysis, yielding utility or preference scores for each attribute. These utility scores can be summed to determine the optimal combination of attribute levels. A conceptual framework of the health consumer’s decision process is presented in Figure 2.

**Figure 2: Conceptual Framework: Health Consumer's Decision Process**



Adapted from Louviere JJ, Hensher DA, Swait JD. Stated Choice Methods: Analysis and Application. Cambridge University Press, 2000. [165]

CA is rooted in welfare economic theory, which states that when asked to choose between two bundles of goods or health services, a rational individual will make the choice that maximizes their own utility. A rational individual is one who makes decisions based on reason [166]. Previous research has shown that CA has acceptable internal validity, internal consistency, and reliability, although further research is required into individual heuristics (decision-making processes) [167, 168]. CA surveys can be very useful in guiding decision making. As the attributes (characteristics) are weighted by their own utility function, their relative importance is revealed [169]. Comparisons between attributes may be performed by calculating the marginal

rate substitution (MRS), that is, the rate at which respondents would be willing to trade between attributes, which can be particularly useful when assessing the trade-offs between strategies. By identifying the value placed on different attributes, CA studies may also shed light on what aspects of a service or intervention can be improved or altered [170].

Currently, cost-utility analyses (CUAs) are the most commonly recommended economic evaluation methodology, using utility as the measure of patient stated preferences [171]. CUAs, however, may leave out important non-health benefits of an intervention, and may not be feasible to apply in complex interventions. CA is a newer methodology in health economics, but has a lengthy history in other fields such as transport economics, environmental valuations, consumer research, and psychology. As CA studies obtain patient preferences for several different attributes of a program or intervention, this method of determining value offers several advantages over other methods of economic evaluation [162]. CA studies may also offer the advantage of being based on community experiences as subjects are often community members, which makes them highly relevant to public policy decisions.

Recently, CA methods have been used to derive preferences, utilities, and WTP in diverse areas. These have included acne treatment [172], lupus management [173], HIV microbicides [174], HIV vaccines [175], insulin formulations [176], cardiac risk assessment [177], post-operative nausea [178], and informal care [179]. CA studies are particularly useful when the process of care is being evaluated in addition to the outcomes of care. When cost is included as an attribute, the MRS for the cost attribute can be used to estimate WTP for an intervention or service. In simpler terms, an individual will experience a decrease in utility by giving up money, but will also experience an increase in utility by obtaining a desired attribute; the amount of money a person is willing to give up to achieve a benefit can be estimated. WTP data may then be used in a CBA [180-182].

## 1.10 Introduction to Cost-Benefit Analysis

Challenges exist in applying traditional cost-effectiveness or cost-utility analyses (CEA and CUA) methodology to telephone information interventions, as it is difficult to value the information which users receive and to define appropriate comparison groups. CEA and CUA are most easily applied to scenarios where the clinical interventions are well defined, where patients receive either intervention A or B resulting in a direct, measurable change in health

status. In the case of TIS, the intervention is not easily defined and varies with each caller, as will the effect on their health status, with the potential that no change in health status occurs.

A societal perspective towards costing in telehealth evaluations is essential, as savings may be incurred for costs related to travel, child care, and lost productivity. The greatest benefit may be mediated through changing patterns of use of other services. For example, by contacting a TIS with a straight-forward question regarding an exposure such as Tylenol, a pregnant woman may save herself a visit to her family doctor or obstetrician.

In a CBA, the dollar value of the difference in costs between programs is subtracted from the difference in program benefits to derive the incremental net social benefit [97]. In this type of analysis, dollars are compared to dollars, whereas in other types of economic evaluations such as CEA and CUA, dollars are weighed against health outcomes. WTP data provide a monetarized form of program benefits. WTP estimates are based on some assumptions, mainly that the consumer is rational and has the full information required to make choices that maximize their utility [183]. WTP is dependent on consumers being able to make informed choices, however this may be compromised if the consumer lacks information or makes decisions narrowly [183].

Using WTP to monetarize program benefits, rather than weighing costs against health outcomes as in CEA and CUA, was considered the optimal methodology in this context. As both mother and child will be affected by the intervention, selecting an appropriate health outcome to measure is difficult, as a single outcome (e.g. birth weight) would not be comprehensive enough to describe the health gains or losses experienced by both affected parties. Multiple health outcomes may be aggregated into QALYs, however there is no current gold standard method for aggregating QALYs across a mother-child pair [184, 185]. Non-health benefits such as reassurance and convenience are also important to quantify and these may be lost when program benefits are measured solely by health outcomes [162]. CBAs using WTP have been performed in both Canadian [181, 186] and American settings [187].

## 1.11 Statement of the Problem: Need for a Cost-Benefit Analysis of TIS

To date, little analysis of the value of TIS has been conducted. Existing evidence suggests that these services play an important role in supporting maternal and neonatal health. The expertise of

TIS counselors is valued in the health care community and TIS are utilized by health professionals. A survey of family physicians in Ontario (700 surveys mailed out, 400 returned and analysed) found that Motherisk was the most commonly cited source of information on pregnancy related drug exposures, with 62% of doctors indicating they consulted Motherisk [188]. While some TIS benefits have been described, the non-health benefits associated with TIS, such as reassurance and convenience, have not been assessed, and women's preferences for teratology counseling have not been directly measured.

A formal economic evaluation weighing the costs and benefits of TIS has not yet been conducted. Preliminary evidence suggests that TIS offer health care cost savings [8, 189]. It is difficult to conduct a traditional CEA or CUA of these services as the information provided by TIS may be one component in a patient's complex health decision-making process that results in changes to health care service utilization and improvement in health outcomes for the mother and fetus [159]. Additionally, quantifying health utilities and improvements in health outcomes to the mother and her offspring in a traditional manner is complex as more than one individual is involved; such analyses have been under explored. Information regarding the economic benefits of TIS, however, is highly desirable and important for improving health care resource allocation processes. Economic benefits may also be measured using WTP methodologies.

## 1.12 Study Rationale

Telephone-based programs have previously been found to be effective in improving health outcomes. Economic evaluations of health care programs require measurement of program benefits. Measuring program benefits in terms of health outcomes is a challenge in the context of an information intervention in pregnancy. Program benefits may be appropriately measured using willingness-to-pay methodology. Assessing preferences for non-health benefits such as convenience and process utility may be important to capture in an evaluation of a telephone-based program. Discrete choice experiments provide a useful method of evaluating preferences for health care program attributes including non-health benefits, and can also yield WTP data.

An economic evaluation of TIS has not yet been conducted and some services have difficulty maintaining ongoing funding. Preferences for teratology counseling and WTP for TIS have not yet been examined. A DCE will provide preference information and can also be used to estimate WTP for teratology counseling. Therefore a CBA of a single TIS consultation using WTP as the

measure of program benefits was conducted. Data on preferences for TIS and family practice characteristics may also help to improve service delivery.

### 1.13 Hypothesis and Research Objectives

It was hypothesized that a counseling encounter with TIS regarding anti-depressant use during pregnancy provides a positive net benefit, measured in dollar terms, compared to a standard encounter with a family physician. The overall study objective is to conduct a cost-benefit analysis of an individual TIS consultation regarding anti-depressant use during pregnancy. There are three specific study objectives:

1. To determine the structure, functions, and operating costs of North American TIS.
2. To determine public preferences and willingness-to-pay for TIS and physician care attributes using a discrete choice experiment.
3. To compare willingness-to-pay for a TIS and physician consultation to their respective program costs in a cost-benefit analysis.

### 1.14 Thesis Organization

The thesis will be comprised of five chapters following the multiple manuscript format. This first chapter has served as an overall introduction to the thesis topic. Chapter two describes a survey of TIS in North America and around the world. This survey provided important costing information for the CBA. Chapter three describes the discrete choice experiment conducted to determine public preferences and WTP for teratology counseling. Chapter four contains the CBA, using the program cost information from chapter two and the monetarized benefits from chapter three to calculate incremental net benefit. Chapter five provides an overall discussion and conclusion of this work, and suggestions for future directions. Versions of chapters one and two have been previously published [189-191]. It is planned to submit two manuscripts based on chapters three and four to appropriate health economics journals.

## 2 Chapter 2: Survey of TIS

### 2.1 Introduction

This chapter describes a survey of North American and international Teratology Information Services (TIS). The purpose of this survey was to obtain descriptive information regarding TIS operations and budgets. This data was used to estimate TIS costs in the cost-benefit analysis. Survey results will be presented and their implications discussed.

#### 2.1.1 Background and Rationale

Teratology Information Services (TIS) provide women and their caregivers with vital information on prenatal exposures to a variety of agents. Improving maternal health during pregnancy can have long-term impacts on the infant and correspondingly, subsequent health care costs. In Chapter one, a summary of the existing evidence of the effect of TIS on maternal and neonatal health was provided. Information received from TIS can prevent congenital malformations, unnecessary pregnancy terminations and occupational risks. TIS support optimal nutritional supplementation and drug therapy regimes during pregnancy and breastfeeding. TIS also improve risk perception and facilitate knowledge transfer and translation [189].

Evaluations of the cost-benefit of counseling are limited. The economic benefits of TIS have not yet been evaluated. The first step in conducting an economic evaluation of TIS is to create a service model of TIS, and in order to do this information regarding the structure and operations of TIS is required. The objective of this study was to conduct a survey of all TIS to obtain essential inputs, including costs, for a service model to assess the cost-benefit of TIS.

#### 2.1.2 Research Objectives

The primary research objective of the survey was to determine the structure and operations of all TIS in North America. The secondary research objective was to determine the structure and operations of all known TIS operating internationally. The third research objective was to compare practices at North American and international TIS.

## 2.2 Methods

### 2.2.1 Study Design

This study was a cross-sectional survey of all known TIS. Completion of the survey served as consent to participate. The study was approved by the Research Ethics Board of the Hospital for Sick Children (HSC).

### 2.2.2 Survey Participants and Sample Size

Directors or managers of individual TIS were selected as the survey respondents, as they are the best qualified and informed to describe the structure and functions of TIS. There were no expected special issues or risks to participation. The sample size for the North American group was fixed based on the enrollment of all North American TIS, estimated at 18 at the time the survey was conducted. For the international group, all members of ENTIS (European Network of Teratogen Information Services) attending their annual meeting were contacted and individual members of known TIS were contacted by email, therefore there was no fixed sample size (see section below for recruitment methods).

### 2.2.3 Recruitment of Survey Participants

The potential respondents were contacted by RH before the 19<sup>th</sup> International Conference of the Organization of Teratology Information Specialists (OTIS) in Tucson, AZ in June, 2006, using publicly available contact information from OTIS. The survey was introduced in a platform presentation and each TIS was given a study package containing the survey and a stamped, addressed envelope. The survey was self-administered by the respondents, who were self-identified as the manager or director of their respective TIS. No compensation for participation was provided. Respondents were encouraged to contact the study coordinator with any questions.

For the international group, the survey was described in a platform presentation at the ENTIS 18<sup>th</sup> International Conference in Helsinki, Finland in June, 2007. Conference attendees were offered a study package containing the survey and a stamped, addressed envelope, or were given the option of completing and returning the survey electronically. TIS in Asia were contacted individually by email and provided with an electronic version of the survey.

## 2.2.4 Privacy and Confidentiality of Survey Participants

Each returned survey was given a number code which was used for identification purposes. No personal information was included in the electronic database. The database was stored in a password protected Microsoft Excel© file on RH's password protected computer. The paper copies of the completed surveys were kept in Dr. Wendy Ungar's research office, which is kept locked. The paper copies of the completed surveys and all electronic databases will be retained until five years following the completion of the study publications, at which point they will be destroyed as per HSC policy.

## 2.2.5 Informed Consent Process for Survey Participation

Written informed consent was not required as the survey was administered to health care workers and is of minimal risk, and therefore meets the requirements for waiving written informed consent as outlined by the Tri-Council Policy Statement on Informed Consent, Section Two [192]. Completion of the survey served as consent to participate.

## 2.2.6 Development of the Survey Instrument

The survey was designed to capture the clinical and research activities of TIS, as well as their structure, operations, funding, and budget. The survey was pilot-tested with experts in TIS at the Research Committee Meeting of OTIS in January, 2006. The survey was reviewed for face and content validity and was revised several times to minimize sources of error or bias. The survey is presented in Appendix 4.

## 2.2.7 Data Collection

The survey asked respondents to provide current information in seven categories: description of respondent, services, staffing, operations, data collection, knowledge transfer activities, and additional information, such as alternative information sources existing in their communities.

## 2.2.8 Data Analysis

The data were entered and maintained as a Microsoft Excel© program. The data were summarized using descriptive statistics. Means and standard deviations (SD) were calculated for normally distributed continuous data and medians and maximum-minimum ranges were calculated for continuous skewed data. Frequency distributions were calculated for categorical

data. Several questions were open ended, and the text was examined for themes and patterns. Pearson correlation coefficients ( $r$ ) were calculated for variables of interest. Spearman's rank correlation coefficients ( $\rho$ ) were also calculated to address skewness in the data, using wessa.net Free Statistics Software [193]. The number of calls per week was multiplied by 52 to give the annual number of calls. The annual budget was divided by the annual number of calls to yield an estimate of the cost per call.

Comparisons were made between OTIS and ENTIS responses using SPSS®. For normally distributed continuous data, a two-tailed student's t-test was performed. For continuous skewed data, responses were compared with the Mann-Whitney U test. For categorical responses, a two-tailed Fisher's exact test was performed. Given that sample sizes were limited by the number of TIS in existence, it was expected that type II errors were possible. Ninety-five percent confidence intervals (95% CI) were calculated to better examine overlap between point estimates.

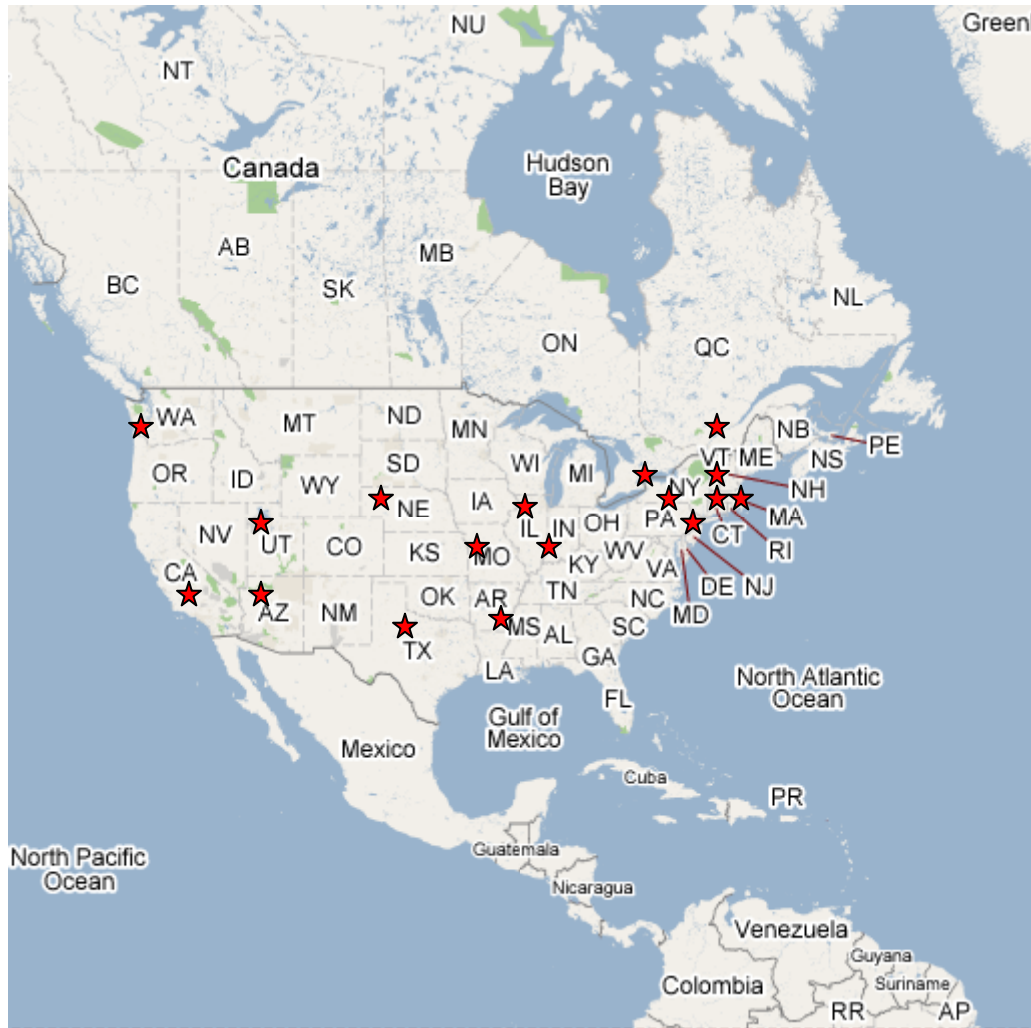
As the Canadian and U.S. health care systems operate differently, TIS in these jurisdictions likely operate differently as well, which makes combining the two countries into a North American cohort problematic. Therefore a sub-group analysis was performed where the Canadian TIS were removed from the OTIS responses and the international responses were compared to responses from the U.S. alone.

Budgets and other monetary responses were provided in varying currencies. Currencies were converted into U.S. dollars using the exchange rate for the date on which the completed survey was returned.

## 2.3 Results

Sixteen American and two Canadian TIS completed and returned the survey, representing all known TIS currently operating in North America. Figure 3 shows the states and provinces with participating TIS.

**Figure 3: States and Provinces with TIS**



\*Two TIS located in New York State.

In the international group, 22 TIS in 16 countries were approached for participation, including TIS in the regions of Central Europe, Northern Europe, Eastern Europe, the Middle East, Asia, and Australia (the ENTIS website currently lists 31 members in 16 countries). Two TIS declined to participate; one TIS claimed to not have sufficient time available to complete the survey, and one was a new TIS that stated they would not have adequate data to report. Four TIS did not reply to emailed participation requests, and were assumed to have declined participation. A total of 16 TIS from 12 countries completed the survey.

### 2.3.1 Services

Respondents were asked to rate service goals from one (least important) to five (most important). The goal ranked as most important by the North American group (hereafter referred to as the Organization of Teratology Information Specialists group, OTIS) was “correction of risk misperceptions and reassurance”, followed by “prevention of unnecessary pregnancy terminations due to high risk perception” (Table 3). Other important goals were “prevention of malformations caused by teratogens” and “education of other health care professionals on teratology”. The most frequently top rated two goals in the international group were also “correction of risk misperceptions and reassurance” and “prevention of unnecessary terminations due to high risk perception.” There was a significant difference in the importance of the rating of “prevention of fetal alcohol syndrome (FAS) specifically”, with OTIS more frequently giving this goal a high importance rating compared to international TIS.

**Table 3: Response Options and Frequencies for Teratology Information Service Goals**

<b>GOALS</b>	<b>INTL**</b>	<b>OTIS**</b>	<b>P<sup>+</sup></b>
Correction of risk misperceptions & reassurance	16 (100%)	17 (94%)	NS
Prevention of unnecessary pregnancy terminations due to high risk perception	16 (100%)	16 (89%)	NS
Prevention of malformations caused by exposure to teratogens	13 (81%)	15 (83%)	NS
Support of adequate pharmacotherapy in pregnancy & lactation	12 (75%)	11 (61%)	NS
Education of other health professionals on teratology	10 (63%)	15 (83%)	NS
Counseling on exposures in lactation	9 (56%)	11 (61%)	NS
Prevention of Fetal Alcohol Syndrome (FAS) specifically	2 (13%)	10 (56%)	<0.01
Prevention of genetic malformations	2 (13%)	5 (28%)	NS

<sup>+</sup>Chi-square test

\*Values presented as counts (percentages in parentheses)

\*\*INTL=International TIS, OTIS=North American TIS

NS= not significant

Respondents were asked about their main counseling inquiries, as a percentage of their total counseling time (Table 4). In both groups, the most frequent inquiries were regarding medications followed by exposures during lactation. Inquiries were spread amongst numerous categories. In addition to those listed in the survey, respondents added other inquiry categories, including cosmetics/beauty products (added by four TIS), radiation (three), food/vitamins

(three), and paternal exposures (three). The proportion of calls regarding medications was significantly larger amongst the international TIS compared to OTIS. There were also significant differences in the percentage of inquiries regarding drugs of abuse, alcohol, herbal products, and exposures in the workplace, with more of these types of inquiries coming to OTIS.

**Table 4: Percent of Time Spent Counseling on Different Topics**

COUNSELING TOPIC	INTL**		OTIS**		P*
	Mean % of time (SD)	95% CI	Mean % of time (SD)	95% CI	
Medications	60.4 (18.8)	51.2-69.6	43.5 (14.1)	36.8-50.2	0.017
Exposures during lactation	14.7 (13.8)	8.0-21.5	10.7 (13.7)	4.3-17.3	NS
Infections	3.3 (3.8)	1.4-5.1	4.5 (2.9)	3.2-6.0	NS
Chemicals	2.8 (2.8)	1.4-4.2	3.1 (2.5)	1.9-4.2	NS
Drugs of abuse	2.7 (3.6)	1.0-4.4	4.6 (3.3)	3.1-6.2	0.033
Folic acid	2.3 (3.2)	0.7-3.8	2.0 (2.6)	1.0-3.4	NS
Environmental agents	2.2 (2.2)	1.1-3.3	3.8 (4.2)	1.7-5.7	NS
Vaccinations	2.1 (1.6)	1.3-2.9	3.5 (2.6)	2.4-4.8	NS
Herbal products	2.0 (2.6)	0.7-3.1	3.7 (2.7)	2.6-5.1	0.027
Exposures in the workplace	1.6 (1.3)	1.0-2.2	5.7 (5.7)	3.0-8.5	0.002
Alcohol	1.6 (1.6)	0.8-2.4	4.2 (3.5)	2.7-6.0	0.014
Genetics	1.6 (5.0)	0.0-4.0	3.6 (8.3)	0.0-7.7	NS
Nausea & vomiting	1.1 (1.7)	0.2-1.9	1.0 (1.8)	0.2-1.9	NS
Smoking cessation	0.8 (1.4)	0.2-1.5	2.8 (3.3)	1.3-4.4	NS

\*Mann-Whitney U test

\*\*INTL=International TIS, OTIS=North American TIS

NS= Not significant; SD= Standard deviation; CI = Confidence interval

The majority of working time at TIS was spent providing counseling over the telephone (see Table 5). In the North American group, the second most time-consuming activity was education of other health care professionals on teratology, followed by faxing material to physicians, and mailing material to patients. Overall there were no significant differences in time spent performing various tasks between OTIS and international TIS, except that OTIS spent more time sending material by fax to physicians.

**Table 5: Time Spent Offering Various Services**

SERVICE	INTL**		OTIS**		P*
	Time Mean % (SD)	95% CI	Time Mean % (SD)	95% CI	
Telephone counseling	56.3 (31.0)	41.1-71.5	61.0 (23.2)	47.6-69.0	NS
Material by mail for physician	14.5 (25.1)	2.2-26.8	1.9 (3.3)	0.4-3.5	NS
Clinic visits for women	8.7 (15.2)	1.2-16.1	4.4 (7.4)	1.0-7.8	NS
Education for other health providers	6.8 (5.8)	4.0-9.6	9.3 (6.8)	6.1-12.4	NS
Material by mail for patient	3.8 (5.6)	1.1-6.5	5.2 (5.9)	2.3-7.5	NS
Diagnosis/testing of infants	2.3 (7.5)	0.0-5.9	1.4 (4.1)	0.0-3.3	NS
Material by fax for physician	2.2 (2.9)	0.7-3.6	7.1 (6.3)	4.2-10.0	0.002
Material by fax for patient	1.7 (2.8)	0.3-3.0	1.3 (2.0)	0.4-2.2	NS
Genetic testing	0.7 (2.5)	0.0-1.9	2.5 (8.5)	0.0-6.4	NS

\*\*INTL=International TIS, OTIS=North American TIS

NS=Not Significant; SD= Standard deviation; CI= Confidence interval

### 2.3.2 Staffing

In the OTIS group, the median number of full time equivalents (FTEs) employed was 2.15 (range 0.15-12.5). The median total number of employees (both full and part time) was three (range 1-12.5). Eleven TIS employed telephone counselors (of these TIS, median 1.0 FTEs). Ten TIS employed managers/directors (median 1.0 FTEs), nine TIS employed genetic counselors (median 1.0 FTEs), nine TIS employed secretaries (median 0.35 FTEs) and three TIS employed research assistants (median 2.0 FTEs). Other permanent paid staff members listed by individual TIS included a nurse, a toxicologist, an information technologist, clinical fellows, a psychologist, and a psychometrist. The Pearson correlation coefficient between FTEs and calls per week was  $r=0.85$  ( $p<0.01$ ). The Spearman correlation coefficient between FTEs and calls per week was  $\rho=0.59$  ( $p=0.013$ ).

In addition to these regular employees, North American TIS reported working with a median of three other HCPs and/or experts. The most common collaboration was with a geneticist, reported by 13 TIS (seven TIS on a consultant basis, one for research, and five for patient care and/or referrals). Other commonly involved specialists included obstetrician/gynecologists (consulted

by five TIS, sent referrals by two), pediatricians (consulted by three TIS, sent referrals by two, and used for dysmorphology exams by one), toxicologists (consulted by six TIS), pharmacists (consulted by five TIS), infectious disease specialists (consulted by four TIS, used for patient care and/or referral by two) and epidemiologists (engaged in research by two TIS and consulted by three). Payment for these experts' services came from different sources, including fee-for-service and hospital budgets.

Many different types of students and trainees worked at North American TIS, for varying lengths of time and in various roles. The median number of students working at TIS each year was 3.5 (range 0-55). Medical students and genetic counseling students were the most common type of student working at TIS (both hosted by nine TIS). Seven TIS hosted clinical, research, or post-doctoral fellows, six hosted pharmacy students, four hosted undergraduate and master's students, three hosted PhD students, two hosted nursing students, one hosted midwifery students and one hosted sonography students.

A mean of 4.0 (SD 2.3) full time equivalents (FTEs) were employed by international TIS. The most common type of employee was telephone counselor (employed by 11 TIS; of these, mean 1.7 FTEs per TIS); secretaries (employed by 11 TIS; of these, mean 0.9 FTEs per TIS); and managers (employed by 10 TIS; of these, mean 0.7 FTEs per TIS). It was found that telephone counselors were often physicians or pharmacists. No significant differences were found between OTIS and international TIS in terms of number and type of staff per TIS. In the subgroup analysis, a significantly smaller number of genetic counselors (GC) were found to work at international TIS compared to American TIS (of four international TIS with GC, mean FTEs was 0.4; of nine American TIS with GC, mean FTEs was 1.0;  $p=0.05$ ).

International TIS reported working with a median of 5.5 external professionals (range 0-40) in addition to their regular employees, for various purposes including research, consultation, and patient care. The most common types of external professionals consulted were pediatricians and epidemiologists (reported by seven TIS), obstetricians/gynecologists (six), and geneticists and infectious disease specialists (five). No significant difference between the OTIS and international groups was found in these responses.

Eleven international TIS reported hosting students. Of these, a median of two students per year worked at the TIS (range 0.3-12). This was fewer than the number of students hosted per year by OTIS, although not significant at the 5% level (median 3, range 0-55,  $p=0.08$ ).

### 2.3.3 Operations

The majority of North American TIS (12/18) were located in teaching hospitals in a variety of departments, including genetics (four), obstetrics (three), pediatrics (two), clinical pharmacology (two), and pharmacy (one). Other TIS locations included not-for-profit agencies (two), university (one), physician's office (one), community hospital (one), and department of health (one). Similarly, the majority of international TIS were located in teaching hospitals (12/16) in a variety of departments, including obstetrics (three), clinical pharmacology and toxicology (two), pediatrics (two), poison control (two), medical toxicology (one), perinatology (one), and pharmacy (one). Other international TIS locations were government health agencies (two), public health agency (one), and university affiliated with a teaching hospital (one).

#### 2.3.3.1 Referrals to TIS

Callers from the public were referred to OTIS by numerous sources. Two TIS only counseled HCPs. Of these two TIS, one was able to provide a break down of referral sources. Of the 17 TIS that provided data, the most common referral source was physicians (mean 44.0%, SD 24.9), followed by nurses (mean 12.1%, SD 11.3), self-referral (mean 8.1%, SD 12.5), midwives (mean 6.8%, SD 7.7), internet (mean 5.6%, SD 7.8), and advertising (mean 5.6%, SD 9.2). Other sources of referral (all means less than 5%, in descending order) included: poison control center, lactation consultant, family/friends, adoption agency, pharmacist, substance abuse program, the U.S. WIC program (Special Supplemental Nutrition Program for Women, Infants, and Children) and abortion clinics. Other referral sources added by TIS included March of Dimes (added by three TIS), Planned Parenthood (two), repeat callers (two), prenatal classes (one), private health insurance company (one), public health (one), government agency (one), genetic counselors (one) and social workers (one).

Seventeen North American TIS indicated that they will refer callers to other HCPs and services if a need was perceived. Of calls that were referred, callers were most often referred to obstetricians/gynecologists and GCs (both listed by 12 TIS). Other common referral destinations

included perinatologists (eight), pediatricians (seven), and social services, sonologists, and toxicologists (all listed by six TIS). Callers were also referred to neurologists (listed by five TIS), psychologists (four) and neonatologists (three). Other referrals listed included geneticists (listed by two TIS), local health departments (two) and occupational health specialists (two). The following referral destinations were each listed by one TIS: psychiatrist, paternity testing facility, family doctor, nurse midwife, La Leche league, health insurance companies, prenatal class, the WIC program, Lead Paint Hotline, National Pesticide Information Center, drug treatment program, AIDS services, U.S. Centers for Disease Control (CDC) travel information, pregnancy registry, smoking cessation program, and family planning program.

Callers were mainly referred to international TIS by physicians (mean 42.2%, SD 26.6) or by themselves (self-referral mean 24.8%, SD 30.3). Other referral sources included pharmacists (mean 5.5%, SD 8.1) and the internet (mean 5.5%, SD 8.4). Referral sources displaying means less than 5% were, in descending order: midwives, lactation consultants, family/friends, media, nurses, advertising, poison control, abortion clinics, adoption programs and foster care programs.

International TIS were asked to what programs or HCPs they might refer callers. Nine TIS indicated that they would refer callers; some indicated that this was an occasional occurrence or might only be done if requested by the caller. If referrals occurred, they were most often to an obstetrician/gynecologist (reported by seven TIS), neurologist (six), perinatal psychiatrist (five), psychologist (five), GC (four) and pediatrician (four). Two TIS reported they would refer callers to specialists in radiation dosimetry, and two TIS also listed lactation consultants as a referral destination. Individual TIS reported that they might refer to the family physician or to the prescriber of the medication. No referrals were reported to occur to social services, whereas amongst the North American respondents, six TIS reported that they refer callers to social services.

### 2.3.3.2 Caller Categories

Respondents were asked to identify the time spent counseling different groups of callers (Table 6). The most frequent caller group to international TIS was pregnant women, followed by physicians and breast-feeding women; these three groups together represented the majority of calls to TIS. Caller groups to OTIS appeared more varied, with OTIS receiving more calls from nurses, other HCPs, and prospective adoptive parents than the international TIS. It should be

noted that one international TIS exclusively counseled women, and one international TIS exclusively counseled HCPs. Other caller groups added by North American TIS were GCs (two), midwives (one), and other TIS (one). Overall, a mean of 33.5% (SD 23.9) of calls were from HCPs and 66.5% (SD 23.9) were from the public in the OTIS group.

**Table 6: Groups counseled by TIS**

GROUPS COUNSELED	INTL**		OTIS**		P*
	Mean % of time (SD)	95% CI	Mean % of time (SD)	95% CI	
Pregnant women	39.2 (26.0)	26.5-52.0	46.8 (22.8)	36.3-57.3	NS
Physicians	28.1 (28.8)	14.0-42.2	11.6 (8.6)	7.6-15.5	NS
Breast-feeding women	11.9 (13.5)	5.3-18.5	7.5 (10.2)	2.8-12.2	NS
Women planning pregnancy	8.5 (7.6)	4.8-12.2	7.1 (5.6)	4.5-9.7	NS
Pharmacists	3.1 (4.3)	1.0-5.2	4.3 (11.3)	0.0-9.6	NS
Spouses/partners	2.3 (3.4)	0.6-3.9	2.3 (2.0)	1.4-3.2	NS
Nurses	1.7 (2.0)	0.8-2.7	9.7 (8.3)	5.9-13.5	0.005
Other health care providers	1.3 (1.9)	0.4-2.3	5.0 (5.6)	2.4-7.6	0.030
Lactation consultants	1.2 (1.8)	0.3-2.0	1.2 (2.6)	0.0-2.4	NS
Family members of pregnant women	1.1 (1.7)	0.2-1.9	1.0 (1.3)	0.4-1.6	NS
Family members of breast-feeding women	0.8 (1.7)	0.0-0.5	0.3 (0.5)	0.2-1.9	NS
Prospective adoptive parents	0.0 (0.1)	0.0-0.0	1.7 (3.0)	0.3-3.1	0.080

\*Mann-Whitney U test

\*\*INTL=International TIS, OTIS=North American TIS

NS= Not significant; SD= Standard deviation; CI = Confidence interval

### 2.3.3.3 Call Volume

The median number of calls per week was not significantly different between international TIS (median 50, range 5-400), and North American TIS (median 20, range 3.5-600). However, a significant difference in calls per week was found in the subgroup analysis (U.S. median 17, range 3.5-250; p=0.04). The reported average length of time per call was very similar between international TIS (median 10 minutes, range 4-60) and North American TIS (median 10, range 5-62). Many TIS noted that the time varies depending on the nature of the call. In the OTIS group, eight TIS reported that they follow up with their callers, two TIS followed up all pregnant callers, one TIS followed up all callers exposed to potential teratogens, and the remainder followed up callers who were enrolled in research studies. Fourteen international TIS reported

following up their callers. The nature of follow up varied; some TIS followed up with almost every caller while others focused on callers who had been enrolled in research projects or with pregnant women with a first trimester exposure.

#### 2.3.3.4 Counseling Practices

Reducing anxiety and risk perception has been previously listed as an important goal of TIS. In the OTIS group, 15 TIS reported evaluating callers' risk perceptions and anxieties during counseling. The majority reported no formal method of assessing risk perception and anxiety, but described being sensitive to the caller's emotional state, listening for crying and changes in voice tone and inquiring about what other information they might have already received. One TIS reported evaluating anxiety during clinic visits using a visual analog scale. In the international group, two TIS reported that they evaluated callers' risk perceptions and anxieties during counseling, two did not answer the question and the remainder (12) replied that they did not. The proportion of TIS that responded affirmatively to assessing caller's risk perceptions was significantly different between ENTIS (14%) and OTIS (83%) ( $p < 0.01$ ).

In-person clinic visits were not performed by every TIS. Seven North American TIS reported seeing patients in regular clinics. Amongst these TIS a median of three patients (range 0-75) were seen per week. Eight international TIS reported that they would counsel patients in person in a clinic and amongst these TIS a median of five patients would be seen per week (range 0.06-20). There was no significant difference in the number of patients seen in clinic per week between OTIS and the international TIS.

#### 2.3.3.5 Budgets and Funding

##### 2.3.3.5.1 North American TIS

The median annual TIS budget was US \$69,000 (range \$3,000-\$335,000, 2005 dollars). Five TIS were unable to identify their annual budget, as it was included in a departmental/clinic/hospital budget. Of TIS that were able to provide a budget, the median cost per call was \$42. This number refers to the entire annual budget divided by the annual number of calls. Cost items included in the budget, however, varied widely between TIS. TIS were asked to describe what cost items were included in their budget. For 16 TIS, the budget included salaries and telephone lines. For 13 TIS, the budget included equipment and supplies. For six TIS, the budget included

capital and overhead. Many cost items were donated to TIS, including volunteer time (five TIS), equipment and supplies (five), telephone lines (three), conference travel (three), capital and overhead (three), database access (two), research funding (two), rent (two), secretarial services (one) and educational and promotional material (one). Due to the variation in the cost items included in the budgets, it is difficult to use this data to estimate the cost per call to TIS.

The most common source of funding was state or provincial governments, with ten TIS receiving at least some of their funding from these sources. Six TIS received all their funding from state or provincial governments (for one TIS the money came to the state via a federal grant). Two TIS were primarily funded by federal governments (for the two, comprising an average of 97.5% of the total budget). Five TIS received their funding from the budget of the hospital in which they were located. One TIS was entirely funded by private donations, one TIS received half their funding from the university in which they were located, one TIS was entirely funded by the Maternal and Child Health Consortium and another was almost entirely funded by a charitable organization.

### 2.3.3.5.2 International TIS

Four international TIS were not able to report a budget. This was similar to the proportion of programs in OTIS who were not able to report a budget (5/18). The median budget for the 12 international TIS able to report one was US\$147,143 (range \$21,460-952,815; 95% C.I. \$122,400-430,706). The median budget for North American TIS was US\$69,000 (95% C.I. \$64,746-168,295) which was not significantly different; however the 95% C.I. show that there is not a lot of overlap between the two, demonstrating generally higher budgets amongst international TIS.

Thirteen international TIS were able to provide details of what cost items were covered by their budget (one TIS provided this information even though they could not provide the exact budget). For all 13 TIS, this budget would cover salaries. Other cost items covered included database access (for 11 TIS), telephone lines (ten), equipment and supplies (nine), library services (eight), conference travel (seven), research (four) and capital and overhead (three). Five TIS reported having volunteer time donated to their service.

The most common funding source was hospital budgets, with five international TIS reporting 90-100% of their funding coming from the hospital in which they were located. Two TIS received all of their funding from the federal government, one from the state/provincial government, and one from the municipal/local government. For the remaining TIS, funds were combined from a variety of sources made up of those previously listed (governments, hospitals), as well as research grants, and small amounts from private donors and charitable organizations.

To obtain an approximate estimate of the cost per call, the service's annual budget was divided by their annual number of calls. The mean cost per call in the overall analysis was US\$242 (SD \$575) (€154, SD 365). However, there was a significant outlier, as a large program described in their survey that telephone consultations now represent a minority of their service, and they focus on information for physicians and clinic visits; therefore this program had a very small number of calls and a large budget. When this service was removed from the analysis, the mean cost per call was US\$78 (SD \$99) (€50, SD 63). This is a rough estimation, as indicated in Table 3 a mean of 56% of service time is spent performing telephone counseling.

## 2.3.4 Data Collection and Research

### 2.3.4.1 North American TIS

Seventeen TIS collected patient data. For all TIS that collected patient data, these data included the woman's week of gestation, the date of the last menstrual period, and other details important to evaluating exposure risk (including history and indication for medication use, ultrasound status in the pregnancy, medical history, previous pregnancies and history of birth defects, other medication use, vitamin intake, cigarette use and street drug and alcohol use). Other information frequently recorded was NVP symptoms, paternal exposures, maternal occupation, and a summary of what information was provided to the caller. The state/province of the caller and what prenatal care had been provided were also often recorded. The address and contact information of the caller was sometimes recorded. Information regarding the newborn would be collected if the inquiry was regarding breast-feeding or if the mother and infant were being followed as part of a research project. For breast-feeding inquiries, information regarding the infant's age, health and feeding habits were recorded. Major and minor malformations were most often recorded for research purposes or for retrospective calls. Sources of this information

included maternal report and birth certificates. All but one TIS recorded these data in a computerized database using safeguarding techniques.

The data gathered by TIS were used for research purposes. Six TIS reported contributing patient data towards collaborative OTIS projects and seven TIS reported using patient data for research published by their TIS as well as in collaborations with other groups such as the Center for Disease Control, state health departments and their hospital/university colleagues. Seven TIS reported that they do not regularly participate in research activities.

### 2.3.4.2 International TIS

Ten TIS were able to provide examples of research papers that had been published using follow up data. The proportion of TIS that followed up callers was significantly different between international TIS (88%) and OTIS (44%) ( $p=0.01$ ).

## 2.3.5 Knowledge Transfer Activities

### 2.3.5.1 North American TIS

All but one TIS counseled HCPs via the telephone. TIS also reported teaching and/or training other HCPs (14), medical students (seven), graduate students in specialties including genetic counseling, pharmacology, toxicology, and pharmacy (five), GCs and genetic counseling students (four), residents and fellows in specialties including genetics, obstetrics/gynecology, perinatology (three) and pharmacists (two), university faculty (one), undergraduate students (one), and dental students (one). These teaching and training activities were mainly described as occurring through lectures, rounds presentations, rotations through the service, the production of newsletters and other education materials and conference presentations.

In addition, 11 TIS reported making presentations to stakeholder groups. Stakeholder groups most commonly addressed were community organizations (by nine TIS), women's health groups (seven), government agencies (seven), patient groups (four), hospital administrators (two), foster and adoption agencies (one), substance abuse agencies (one), occupational health specialists (one) and schools (one).

TIS reported contributing to the base of scientific knowledge in this field. Of the nine TIS that reported publishing scientific papers, a median of 19 papers per TIS had been published (range

1-500). One service has been an extremely frequent publisher whose best estimate of published papers in the history of the program was approximately 500. When this outlier was removed from the data set the median became 13 (range 1-36). The Pearson correlation coefficient between the number of papers published and calls per week was  $r=0.90$  ( $p<0.01$ ). The Spearman correlation coefficient was  $\rho=0.55$  ( $p=0.23$ ). Nine TIS reported giving a median of seven poster presentations at conferences in the five-year period prior to the survey (range 1-500). Eight TIS reported giving a median of 12.5 oral presentations at conferences in the five-year period prior to the survey (range 1-500).

### 2.3.5.2 International TIS

A mean of 37% (SD 33) of calls received were from HCPs. Thirteen TIS reported participating in training activities for other HCPs, primarily through medical school courses, lectures, and workshops. Seven TIS reported making presentations to stakeholder groups. International TIS are active in research, with respondents reporting an average of 17 published papers in their group, as well as 5.5 posters and 20 oral presentations. International TIS reported publishing significantly more papers than the U.S. TIS in the subgroup analysis (17 vs. six,  $p=0.023$ ).

## 2.3.6 Additional Information

### 2.3.6.1 North American TIS

TIS were asked to rank the importance of alternative sources of information that a person might use in their region if they did not consult a TIS. Sources were ranked from one (least important) to five (most important). It was found that the most important alternative source of information was a GC (score of four or five reported by 13 TIS) or a family physician (score of four or five: reported by 12 TIS). Other important sources of information were internet (score of four or five: nine TIS), poison control centre (score of four or five: eight TIS), March of Dimes (score of four or five: seven TIS), community health centre (score of four or five: five TIS) and public health office (score of four or five: four TIS). Three TIS also listed pharmacists as an important source of information (score of four or five: three TIS). Although the internet was reported as an important source of information, several TIS commented that this only refers to particular websites offering high quality information. Thirteen TIS operate their own website. All TIS reported that they had not previously conducted a formal economic evaluation of their service.

### 2.3.6.2 International TIS

International TIS were also asked to rank the importance of alternative information sources in their region. Family physicians were ranked as the most important source of information outside of TIS, followed by poison control centre, genetic counselor, and community health centre. One TIS also listed gynecologists and midwives as important information sources. Ten TIS operate their own website. Thirteen TIS reported that they had not previously conducted a formal economic evaluation of their service.

## 2.4 Discussion

### 2.4.1 Discussion of North American TIS Survey Data

Although TIS have been operating for many years, this survey was the first formal evaluation of their practices. This survey highlights that the main goals of TIS are to correct misperceptions of risk, provide reassurance, prevent unnecessary termination and birth defects and educate other health care professionals on the complex teratology field. These services are generally staffed by a few trained professionals whose main activity is providing information and counseling via telephone. The number of calls received per week and participation in research activities varied widely.

The finding that the service goal ranked highest was “correction of risk misperceptions and reassurance,” followed by “prevention of pregnancy terminations caused by risk misperceptions” is in keeping with the understanding that the majority of exposures during pregnancy are not teratogenic, yet provoke great anxiety in pregnant patients [8, 194]. This anxiety has been found to lead to terminations of otherwise wanted pregnancies in Canadian and Italian studies [37, 38]. The importance of changing risk misperceptions at TIS could also be indicative of hesitation on the part of physicians to provide strong reassurance following exposures due to uncertainty or fears of litigation. This theory is supported by the finding in this study that physicians are the primary referral source of callers to TIS, and by a previous study documenting that 91% of physicians who had consulted a TIS reported repeating the information they had received from the TIS to their patients verbatim [85]. A survey of medical professionals who had used a TIS found that 97% thought that it was a useful service [26]. A previous study found that 80% of retail pharmacists would be eager to take on more responsibilities counseling patients if an

independent high-performance information source such as a TIS were available [195]. Overall, the differences between ranked goals were small and in keeping with the original goals stated when OTIS was formed [9].

It was expected that the main counseling inquiry would be regarding medications and there was little variation in the types of inquiries across TIS. Previous studies have also found medications to be the most common inquiry at TIS in both North America and Europe, with other inquiries such as radiation, vaccination, infections, environmental agents, and substance abuse comprising smaller proportions of calls [26, 73, 196].

There was a large variation in the number of full-time employees working at each TIS. The number of FTEs and calls per week were highly correlated. Many TIS indicated that they work with other HCPs in both clinical and research capacities and are also supported by students and volunteers. The amount of inter-disciplinary collaboration and training that occurs at TIS is remarkable; previous reports have also remarked on the overlap between numerous fields and services that is required to adequately perform teratology counseling [73, 197, 198]. The extent to which additional expert support was available may be dependent on the TIS' location. For example, it may be easier to consult a staff pediatrician at no cost to the TIS if the TIS is located within a hospital, or to use students for labour and research if in a university setting. The majority of TIS are located in teaching hospitals, which likely facilitates collaboration and consultation. The difficulty in assigning costs to the external consultations is a limitation of the study and may lead to an underestimation of TIS costs. Questions regarding TIS in-house training practices were not asked, which would have been an important question to have included and could be investigated in future surveys.

While physicians were found to be the primary source of referrals to TIS, referrals came from many sources, making targeted promotion campaigns a challenge. Similarly, a variety of groups are counseled by TIS, although the largest group is pregnant women (mean 46.8%). Women planning pregnancy were an average of only 7.1% of callers, perhaps reflecting the fact that approximately half of pregnancies are unplanned [199]. This proportion was slightly higher than the reported 3-5% of women callers to ENTIS who were planning pregnancy [4]. This report identifies opportunities for TIS to promote awareness of their services amongst professional

groups that may be under-utilizing them, such as lactation consultants (mean 1.2% of calls) and pharmacists (mean 4.3%).

Follow-up of callers varies widely and this is likely due to constrained budgets and time. Follow-up data are important to research and demonstrating program effectiveness. Therefore increased efforts to gather follow-up information may be necessary. It was a limitation of the survey the demographic make-up of callers was not ascertained, although many TIS may not have been able to share such information.

There was variation in budgets, and five TIS were unable to report a specific budget, as separating TIS budgets from departmental and other research budgets was difficult. This demonstrates the overlap between clinical and research activities that occurs at TIS, as well as their multi-disciplinary nature. As TIS are generally part of a department or clinic service in a hospital or university, separating out cost items specifically devoted to TIS is a challenge. A minority of the budget estimates included capital and overhead, which are presumed to be absorbed by another department. Operational costs are also difficult to capture as some telephone counselors work from home. Methods of funding TIS and budget tracking varied. It has been previously noted that having fragmented sources of funding makes TIS vulnerable [198].

It appeared that there were two main types of TIS: 1) services dedicated mainly to teratogen information counseling and staffed by full-time teratogen specialists and 2) services operated part-time by GCs as part of their overall clinic duties. Approximately half of the TIS had one FTE, and the TIS with one or fewer FTEs were generally staffed by genetic counselors. It is important to be aware that there are two main two service provision models in North America, and they might each have unique issues and challenges.

The fee-for-service cost of a consultation with a family doctor in Ontario ranges from US \$31.83 for an intermediate consultation to US \$56.79 for a full consultation [200]. The average cost of a pre-natal visit to a GC in the U.S. has been quoted as between \$175 to \$300 [201]. Both of these costs are from the payer perspective, and therefore do not include travel and productivity costs to the user. The median cost per call to OTIS of \$42 compares favourably with similar services. This estimate, however, is limited by the fact that the budgets provided were comprised of different cost items (e.g. some include research expenses, and some do not), five budgets were not available, and the entire budget is not devoted to counseling practices (telephone counseling

took up a mean of 61% of service time, see Table 2). Any future TIS costing exercises will be limited by a lack of accurate budget data, and it is important to bring awareness to this issue.

Data collection practices were mostly uniform and were similar to data collection methods described by ENTIS and the Council of Regional Networks for Genetic Services [198, 202]. It has been previously described how TIS are uniquely positioned to perform post-marketing surveillance of drugs [93, 203]. It is clear that research and education are a large part of TIS activities, yet there is room for increased research activity especially given that not all TIS participate in caller follow-up. There was variation across TIS in the amount of research performed, yet virtually all services contributed cases to collaborative studies facilitated by OTIS. The high correlation found between number of papers published and calls per week demonstrates the important connection between clinical and research activities at TIS.

Education of other HCPs was the second most common work activity conducted by TIS following telephone counseling (Table 3). Continued education of other HCPs is an important TIS priority as well (Table 2), although many HCPs will still refer patients to TIS rather than provide recommendations themselves [85]. An evaluation of Doctorline, a medical information service for physicians, found that the most common types of inquiries to the service from GPs were regarding pharmacology [149]. This demonstrates that physicians need support in staying up-to-date in the constantly evolving and complex field of pharmacotherapy.

#### **2.4.2 Comparisons between North American and International TIS Survey Responses**

TIS provide counseling on a wide variety of issues, working with multi-disciplinary teams in different settings. While international and North American TIS have many similarities, there are a few interesting differences that may shed important light for the future of this medical specialty. With the exception of FAS prevention, service goals for all TIS were quite similar. Compared to North American TIS, TIS in international settings appear to have more homogeneous caller categories (primarily physicians and pregnant women) and inquiries (primarily medications). North American TIS were utilized by a wider variety of health professionals and were more frequently asked about non-medicinal exposures such as drugs of abuse, herbal products, workplace exposures, and alcohol.

In North America and internationally, services were offered in a variety of environments, departments, and involved a large and varying number of professionals. Both surveys demonstrated that TIS are staffed by a range of professionals with a variety of backgrounds. This is necessary in a complex field that draws on expertise in the areas of obstetrics, pediatrics, pharmacology, epidemiology, genetics, biostatistics, and others. This leads to the question: is there a preferred setting for TIS? TIS have been successful in numerous locations, but it may be necessary in the future to align with a particular department or health care setting in order to foster stability.

There was no significant difference in budgets, number of staff, and length of calls; although the 95% confidence intervals indicated that there may be slightly higher budgets and numbers of staff at international TIS. Internationally and in North America, analysis of costs had to be limited by the ability of TIS to provide accurate budgets, which can be mixed in with departmental budgets and amongst other programs and services. It will be important in the future for TIS managers and directors to accurately track their costs, as this is necessary to assess cost-effectiveness. We found that telephone counselors working at international services were more often trained as medical doctors (MDs). It is likely that MDs might have higher salaries than normal staff. However, given that overall staff numbers are similar and staff salaries are the main expense in providing teratology counseling services, it is logical to expect that budgets would not be very different. There was no difference in length of time per average consultation.

Subgroup analysis revealed that international TIS received significantly more calls per week than TIS in the United States. The reasons for this difference are unclear. It has been previously noted that within ENTIS, there is a large variation in consultations by TIS compared to birth rates. Using birth rate data and the number of consultations performed each year by TIS, it has been found that the rate of TIS consultations per births varied 10-fold between TIS, from 0.012 to 0.14 [93]. Potential reasons for this variability have been suggested, and may include multiple consultations, differences in public awareness and risk perception, and more awareness of women and HCPs about the service. A recent report by a TIS in Brazil that was not included in this survey stated that in a four year period of operation, they received approximately one call per day [204]. Calls were reported to generally last 15 minutes, so it is possible for one counselor to handle several calls in a day. It is important for TIS to be aware of their call volumes and take steps to ensure they are being adequately utilized.

Another notable difference between North American and international programs was the level of participation in research and follow-up of patients. International TIS produced significantly more research papers and oral presentations, and had nearly complete follow-up of callers leading to significant research databases. ENTIS has standardized data collection procedures, which facilitates pooling of data [4]. Such observational databases are of vital importance to assessing drug safety and effectiveness during pregnancy, given that there is a paucity of such data. Recent efforts by the U.S. Food and Drug Administration (FDA) to improve drug labeling have called for pregnancy exposure registry information to be included in labels whenever possible [205], and TIS may be able to play an important role in providing pregnancy registry data. In North America, it appeared that the programs that had higher participation in research were often larger and received more calls per week [190].

Comparisons between health care programs in the U.S. and other industrialized nations must take into consideration the different health care systems and their funding structures. The U.S. provides much of its health care through private health insurance plans, however 18% of Americans currently lack health insurance [206]. Caller identities and the nature of their calls may be affected by the type of access available to prenatal care. It has been found that in countries with universal health care, women start prenatal care earlier yet have fewer prenatal visits over the course of the pregnancy [207]. The effect of differences in prenatal care on the utilization of TIS is unknown. It was interesting that counseling practices in terms of anxiety reduction varied, as international programs were significantly less likely to report assessing risk perception and anxiety. Reasons for this are unclear.

Further differences exist between the U.S., where the majority of North American TIS are located, and Europe, where the majority of international surveys were obtained. The attitudes of the medical community towards alcohol use during pregnancy are different, with Canadian and American physicians routinely advocating complete abstinence from alcohol during pregnancy, while their counterparts in the UK may advise that perhaps one or two drinks per occasion per week is acceptable [208]. This attitudinal difference likely explains the significant differences found between percentage of calls related to alcohol, and the rating of FAS prevention as a service goal. Additionally, in North American society FAS is more common in Native populations, which are not present in Europe [209]. There are also differences in the litigiousness of European and American societies that may affect the way physicians prescribe medications to

pregnant and lactating women [210]. American society is generally viewed as more litigious, largely due to differences in incentives; in the U.S., each party pays their own legal fees, whereas in Europe the loser pays the winners' legal fees, which is seen as a strong disincentive for legal action [211].

### 2.4.3 Limitations

The survey of international TIS was limited by less than complete participation. Six programs declined participation. ENTIS reported 28 members in 2002 [202], and 33 members in 2005 [93]. Only those TIS with representatives attending the 2007 ENTIS meeting and those with previous connections to the authors were contacted. It is possible that there are other TIS that are not known to us. Any conclusions drawn from this survey and comparisons to the North American survey results are limited by the small sample sizes available.

## 2.5 Conclusions

This survey found that presently few staff and little infrastructure are available to provide teratology information to HCPs and the public. A representative North American TIS would have 1-2 employees, performing counseling, research, educational and administrative duties. Based on the expectation of professional salaries for these employees, it appears that the main cost driver for these services is employee salaries, with little money being required for overhead. This makes intuitive sense given the structure and process by which the information is provided. The cost per telephone consultation compared to other health care services, such as family physicians and GCs, was low.

These survey results offers TIS the first ever opportunity to compare practices. While many aspects of services are similar, important differences exist. Inquiries to international programs appear to be more narrowly focused, with many calls coming from physicians regarding medications, while in North America there was a wider spread amongst the types of health care professionals utilizing the service. The nature of inquiries to OTIS more frequently regarded social issues, including adoption and addiction. Services everywhere could improve tracking of budgets. Knowing program costs is a vital first step in determining cost-effectiveness in cost constrained health care systems. Similar proportions of programs, both internationally and in North America, were unable to provide budget estimates, and available budgets varied in terms

of what cost items were included. Follow-up of patients is an important area where North American programs could improve. Increased patient follow-up leads to increased opportunities for research, which serves both to improve knowledge in the field as well as raise the profile of the programs within the medical and academic communities. TIS have emerged in multiple settings with varying staff, which provides the programs with a richness of expertise, however in future it may be important to consider if there is a preferred site for TIS and if standardized training for staff could or should be provided.

Based on these survey findings, it can be recommended that TIS continue to expand their follow-up and research activities. These activities are correlated with service growth and will increase knowledge of TIS amongst researchers and health care professionals. A toll-free national inquiry line is now available in North America, however optimal service delivery will require stable funding. It will be important to critically assess the economic benefit of TIS to recognize their potential value to the population, similar to poison information services and genetic counseling. Increased dialogue between TIS will lead to sharing of best practices and improve the ability of these important programs to support women and health care providers.

## 3 Chapter 3: Discrete Choice Experiment to Assess Public Preferences and Willingness to Pay for Teratology Counseling During Pregnancy

### 3.1 Introduction

#### 3.1.1 Overview

A need exists for experts to help interpret limited and conflicting data regarding the safety of exposures to potential teratogens during pregnancy to members of the public, as medication labeling systems are considered inadequate and many health professionals lack confidence advising in this area [65, 75, 77, 85]. The best method of delivering such teratology counseling services is currently unknown.

Discrete choice survey methods were used to determine public preferences and willingness-to-pay for teratology counseling services. This survey methodology enables the deduction and quantification of preferences through the assessment of trade-offs made between attributes. Discrete choice experiments (DCEs) are one method of eliciting preferences, a field of study more broadly termed conjoint analysis (CA). In a DCE, survey respondents are asked to choose between two service scenarios described by relevant characteristics or attributes, and respondent choices reveal preferences for service attributes. When cost is included as an attribute, willingness to pay (WTP) can be estimated.

DCEs have traditionally been used in the fields of marketing, psychology, and transport research, and have recently been utilized in health care assessments with increasing frequency [169]. DCEs are a stated preference (SP) method. Revealed preference (RP) methods evaluate preferences by observing consumer behaviour. For example, if a person buys an orange rather than an apple, it is observed that the preferred fruit is orange. RP methods, however, are not useful for estimating preferences when a market for the good does not exist [165]. They do provide an accurate depiction of real life behaviour, whereas SP methods are hypothetical. Both RP and SP methods have advantages and disadvantages [212]; an SP approach is most suited to valuing the benefits of telephone-based health information intervention. Another SP method is contingent valuation (CV). In a CV study, survey respondents are asked directly what they would be willing to pay to obtain a benefit [165]. An advantage of a DCE over a CV study is that in

addition to estimating WTP, DCE provides information regarding preferences for specific service attributes. Knowledge of preferences for attributes can be used to inform service design. WTP for non-health attributes such as the process of care may also be estimated using SP methods.

### 3.1.2 Hypothesis and Objectives

It was hypothesized that the quality of the information and counseling provided would be the most important service attribute. There were no specific hypotheses about the directions of preferences for the other attributes that were assessed. There were four specific objectives of the DCE:

1. To determine public preferences for attributes of teratology counseling.
2. To determine the relative importance of the defined attributes.
3. To determine if demographic characteristics of the public such as age, income, education, ethnicity, and number of children influence preferences.
4. To estimate WTP for TIS for use in a subsequent cost-benefit analysis.

## 3.2 Methods

As previously described in sections 1.10 and 3.1.1, a DCE is a survey in which respondents are asked to choose their preferred scenario from a set of scenarios described by specific attributes [165]. There are five key steps in performing a DCE:

1. Selection of attributes and levels;
2. Selection of experimental design;
3. Pilot testing of the survey instrument;
4. Measurement of preferences;
5. Data analysis [165, 213].

A detailed description of each of these steps follows in this section.

### 3.2.1 Selection of Attributes and Levels

Attributes and levels were selected in a multi-stage process. First, a literature review of DCEs in the field of women's health and pregnancy was conducted to determine previously identified attributes of importance and relevance. Second, a list of potential attributes was generated. This list was brought to three focus groups, where the list was rated and other potential attributes were discussed. Finally, the focus group discussions were analyzed and attributes and levels were selected for pilot testing.

#### 3.2.1.1 Literature Review of Discrete Choice Experiments in Women's Health and Pregnancy

One part of the approach to generating attributes and levels was to examine previously identified attributes of importance in women's health care services. As there is little research in the area of preferences for teratology counseling, a more general approach to the literature search was adopted. A search of the literature in the PubMed database was conducted. There was no time restriction. The following search terms were entered in different combinations: "discrete choice experiment," "conjoint analysis," "women's health," "pregnancy," and "teratology." The search revealed 19 previous studies that used DCE methods in the context of women's health and pregnancy. A summary of those studies is provided in Table 7.

**Table 7: Discrete Choice Experiments Evaluating Women's Health Services**

<b>Reference</b>	<b>Topic</b>	<b>Attributes</b>	<b>Survey Respondents</b>	<b>n</b>
Ryan 1997 [214]	Miscarriage management	Level of pain; time in hospital for treatment (tx); time to return to normal household activities after tx; cost to you of tx; complications following tx	Participants in a RCT comparing surgical & medical management of miscarriage	196
Ryan 1999 [169]	In vitro fertilization	Chance of having a baby; follow-up support; wait list time; staff continuity; cost; staff attitudes	Prior patients at an Assisted Reproduction Unit	331
San Miguel 2000 [215]	Menorrhagia treatment	Nights in hospital after intervention; time to return to normal activity; chance of complications; probability of re-tx with conservative surgery; probability of re-tx with hysterectomy; cost	Female hospital workers	146
Longworth 2001 [216]	Intra-partum care	Staff continuity; delivery location; pain relief available; participation in decision-making; probability of transfer during labour	Women attending a maternity unit	257
Hundley 2001 [217]	Intra-partum care	Timing of meeting midwife; pain relief available; monitoring available; room appearance; medical staff involvement; involvement in decision-making	Women using midwife services who are at low obstetric risk	301
McKessock 2001 [218]	Laparoscopic sterilization	Amount of written information; who is consulted; wait time; travel costs	Women undergoing sterilization	232
Taylor 2003 [219]	Induction of labour	Administration method; setting; time from induction to delivery; pain level; delivery type; cost	Pregnant women attending public antenatal clinics	340
Bishop 2004 [220]	Down's syndrome screening	Time in weeks (of test); detection rate; risk of miscarriage	Pregnant women & HCPs	389
Ryan 2005 [221]	Pre-natal testing	Level of information; # of days wait for results; cost	Pregnant women	40
Christofides 2005 [222]	Services after rape	Travel time; HIV prophylaxis availability; # of returns to hospital; medical examination, & counseling skills; provider attitude	Half were post-rape patients, half were community volunteers	319
Lewis 2006	Pre-natal testing	Gestation time in weeks (of test);	Women, HCPs at	632

[223]		accuracy; risk	teaching hospital	
Hall 2006 [224]	Genetic carrier testing	Test recommended by Dr; individual/couple risk assessment; test location; false negative chance; results wait time; cost; risk of being a carrier; risk that affected child has mild symptoms; proportion of people like you that have been tested	Community sample & Ashkenazi Jews	471
Wordsworth 2006 [225]	Cervical cancer screening	Time between smears; time to results; chance of recall; chance of abnormality; chance of dying of cervical cancer; cost	Community sample of women	641
Basen-Engquist 2007 [226]	Cervical cancer screening	Pain; time of results & tx; specificity; sensitivity	RCT participants (optical spectroscopy for dx of cervical dysplasia)	906
Seston 2007 [227]	Emergency hormonal contraception (EHC) services	Opening hours; medical staff seen; cost; wait time for appointment; privacy of consultation; staff attitudes	Women attending contraceptive & sexual health services	269
Petrou 2008 [228]	First trimester miscarriage management	Time spent at hospital for tx; pain level; # of days bleeding after tx; time to return to normal activities; cost; chance of complications	Pregnant women in 1 <sup>st</sup> trimester	1198
Pitchforth 2008 [229]	Intrapartum Care	Care provider; pain relief available; travel time	Women who had recently delivered	877
Bijlenga 2009 [230]	Delivery in moderate risk pregnancy	Maternal health antepartum; time from diagnosis to delivery; delivery process; maternal outcome; neonatal outcome	Community volunteers	97
Pavlova 2009 [231]	Home vs. hospital birth	Assistance during birth; birth setting; influence on decision-making; pain-relief tx; place of delivery; transfer during birth	Nulliparous pregnant women	78
Kruk 2009 [232]	Location of delivery	Distance; cost; provider type; provider attitude; drugs & equipment; free transport	Community sample of women	1203

The attributes of importance identified by these studies will be summarized, as will their study designs. A description of those studies that included WTP is provided in Table 12.

One of the first rigorous DCEs in the area of health was a study assessing women's preferences for different modes of miscarriage management. It was found that there was a general preference

for surgical management rather than medical management (Ryan 1997) [214]. The identified studies were also reviewed for their methodological approaches and recruitment success. In the miscarriage study, respondents were asked to make a discrete choice between two service scenarios. The survey was conducted by mail, with 33% of the mailed questionnaires returned. Income level affected both WTP and preference for time spent in hospital (women with higher income levels wanted to spend less time in hospital) [214]. The study concluded that CA methodology is a useful tool for estimating WTP and utilities [214].

The process of care can sometimes be as important as the outcome of care. Preferences have been assessed for both health and non-health outcomes amongst men and women undergoing in-vitro fertilization (IVF) (Ryan 1999) [169]. A satisfaction questionnaire was mailed to 1146 past IVF users; the 446 people who responded were then mailed the discrete choice survey, and 331 usable surveys were returned. Previous economic evaluations had calculated WTP per live birth, while the goal of this DCE was to determine what non-health attributes were valued by patients in the IVF process. It was found that good staff attitudes were valued more than a 6% increase in the chance of taking home a baby, and that continuity of care was valued at slightly more than a 2% increase in the chance of taking home a baby [169]. In a study particularly relevant to counseling services, a study of women's preferences for the provision of emergency hormonal contraception (EHC) found that respondents prioritized privacy and visiting a service where they would be treated in a sympathetic and non-judgmental manner (Seston 2007) [227]. Women's preferences for counseling services after rape are to have availability of HIV prophylaxis treatment and a sensitive health care provider; these were valued more than travel time (Christofides 2005) [222].

HCPs and patients may have different preferences. A comparison of patient and HCP preferences for attributes of prenatal screening for Down's syndrome found that women and HCPs valued the detection rate of screening tests similarly; however, HCPs valued timing of prenatal tests and risk associated with the subsequent diagnostic test more than women. (Lewis 2006) [223]. Compared to HCPs, women would wait longer and accept a greater decrease in detection rate for a test if it was safer [223]. In a non-pregnancy context, it was found that patients placed a greater value on prognosis information in cardiac risk assessment compared to physicians [177].

As previously discussed in section 1.4, methods of economic evaluation that only value health state improvements or QALY gains may be under-valuing the multiple dimensions of health care, such as information or reassurance [177, 233]. In a WTP study involving pregnant women, it was found that 26% of the value attached to an ultrasound test was related to information having no decisional prognostic significance, and 37% of the value related to information useful to the patient but not the doctor [233]. This study also found that women were willing to pay USD \$706 on average for an ultrasound in a normal, uncomplicated pregnancy, to obtain only seven items of information (limited to health of baby, health of mother, due date, twins, sex, image, and snapshot) [233].

These studies demonstrate that taking account of patient preferences is an important part of planning service provision, that patients place a high value on information even if it does not have a direct impact on prognosis or on health outcomes, and that patient preferences may differ from those of their HCPs. These preference studies were mainly completed in European settings, therefore these preferences may not be generalizable to other jurisdictions. Common attributes amongst the 19 studies are presented in Table 8.

**Table 8: Common Attributes in Discrete Choice Experiments of Women’s Health Services**

<b>Attribute</b>	<b># Studies</b>
Waiting/travel/treatment time	13
Cost	11
Pain level/treatment available	8
Procedure success/accuracy	6
Type of medical staff seen	5
Setting	4
Staff attitudes	4
Continuity of care	3
Involvement in decision-making	3
Chance of complications	2

Preferred attributes included non-judgmental and positive staff attitudes, privacy, continuity of care, and participation in decision-making. Collectively, these studies demonstrate that the processes of care as well as the outcomes of care are important in maternal health services, particularly staff attitudes and sensitivity. These findings were used to inform the selection of attributes for pre-testing in the focus group discussions.

### 3.2.1.2 Pre-selected Attributes for Focus Group Testing

In selecting the attributes for the discrete choice survey, it was considered that the primary alternative source of information would be a family physician consultation. This assumption was based on two previous surveys that demonstrated that telephone health line users would most commonly consult a family physician if the telephone service was not available. Family physicians were also listed as the most important alternative source to TIS in the survey of TIS (chapter two). In a survey of users of a telephone nursing service, approximately one third of callers reported they would have otherwise visited a general practitioner (GP) if the service were not available [150]. Similarly, 60% of callers to a rheumatoid arthritis nursing line stated they would have visited a GP if the service were not available [151]. An Australian survey found that GPs were the most frequently used formal source of information about using medications during pregnancy [234]. Awareness of TIS may be low. It is therefore reasonable to expect that a woman would consult her family physician with a drug safety question as the front-line HCP. It is acknowledged that pregnancy may result in different health care behaviours, potentially limiting the survey's generalizability. It is possible other avenues of information would be used, such as consulting pharmacists or internet searches. A doctor's visit was selected as this is generally considered to be the gold standard source of health care information and was therefore thought to be the optimal service comparator.

Based on the findings of the literature review and a consideration of the main differences between TIS and physician services, five attributes were initially considered for evaluation. The attributes and their rationales are described below.

#### *Attribute 1: Person you contact*

It is unknown whether a woman would prefer speaking with her physician, any physician, or a non-physician who is an expert in the field of teratology. A previous study of primary care preferences found that seeing one's own GP was preferred over seeing a health care team consisting of doctors and nurses only by older and very sick respondents [235]. Another study of GP after hours care found that respondents were indifferent to whether the doctor was their own regular doctor or another family doctor [236]. The framing question in that study was of an emergency situation where a child had respiratory distress, so the importance of whether the

doctor is someone known to the patient may vary depending on the urgency of the medical situation. A study of preferences for EHC services found that women preferred to see a nurse or doctor rather than a pharmacist [227]. Two studies of primary care preferences (one regarding treatment of a minor illness, and one regarding out-of-hours care) found that people were willing to wait longer to see a doctor versus a trained nurse, however in one study many respondents were happy to see a nurse if other aspects of the consultation were improved [237, 238]. Perceived skill of the provider was the most important attribute in determining patient satisfaction in one study [239].

A study of preferences for continuity of care in family practice found that patients were willing to see unfamiliar practitioners for minor familiar symptoms, however if they were consulting for a new unfamiliar condition, they were willing to trade several days of waiting time to see their regular care-giver [240]. A survey of liver transplantation patients found that they were willing to trade a reduction in treatment success for continuity of care with the same staff [241]. A similar finding was obtained in the DCE of IVF [169].

*Attribute 2: Method of contact*

It is unknown if there is a benefit to speaking to a HCP in person or if the same information can be adequately communicated by telephone. A study of patient preferences for HIV testing found that respondents had lower preferences for in-person information counseling compared to reading a brochure containing the same information [242]. Anonymity may be important when dealing with sensitive information. On the other hand, human interaction may be an important part of a counseling experience.

*Attribute 3: Time you wait to receive information*

Several previous studies have found that patients value shorter waiting times [213, 218, 225, 227, 241-243]. This is also one of the more obvious differences between TIS and physician care. The extent to which survey respondents would be willing to trade waiting time for other counseling attributes is unknown.

*Attribute 4: Cost to you*

Defining the cost attribute is a challenge when surveying Canadian respondents, for whom the majority of health care is paid for by government sources. Primary care is almost entirely covered through national insurance paid for by taxes, whereas other benefits, particularly vision, dental, and pharmaceuticals, are largely paid for by employer-provided insurance with co-pays (REF). Previous studies have determined, however, that Canadians are willing to pay for health care out of their own pockets. WTP has been evaluated in Canadian settings for diverse health services including Alzheimer's medications [244], choice of treatment locations [245], inhaled insulin devices [246], wait time reduction for cataract surgery [247], and medication adverse event reductions [248]. A comparison of WTP for reductions in risk of death between Canadian and U.S. respondents did not find a statistically significant difference between the two settings, so it is possible that differences between the two countries may be small [249]. Cost did not influence choices in the study of preferences for EHC services (Seston 2007) [227].

*Attribute 5: Helpfulness of information provided*

Whether or not the information provided addresses the drug safety question adequately is of crucial importance. Health care quality has been ranked as more important than access to care in a Bulgarian study [250]. Correctly defining attributes related to the quality of counseling and aspects of the health provider relationship may be difficult, as there are many features whose definitions may overlap. For example, an attribute related to helpfulness may be whether or not the counselor listens to the questions being asked. One study found that whether the doctor listened was the most important attribute in choosing primary care [236]. Similarly, "being able to talk to your doctor" was chosen as the most important attribute in the doctor-patient relationship [251]. An evaluation of GP consultation experiences found that "larger increases in utility were associated with changes on 'doctor listens' attribute, followed by easily understood information, a shared treatment decision, more information and longer consultation." [252] In the EHC study, women were willing to pay a mean of £25 to be seen by a staff member who was sympathetic and non-judgmental rather than a staff member who was non-sympathetic and judgmental [227].

### 3.2.1.3 Focus Group Testing

Focus group discussions are an appropriate and oft-used method for aiding the development of a research instrument [253]. Focus groups provide rich qualitative, experiential data that can be used to explain and describe choice behaviour. Such personal accounts are particularly important in generating attributes for a DCE. As only a small number of attributes are generally used, determining the most pertinent ones is a very difficult task. As previously mentioned, the preferences of HCPs may be different from patients or the public at large, therefore focus group discussions with community volunteers are of particular importance, especially for evaluations such as this where the intervention is a public good. Using focus group inputs helps to root the study within community values.

### 3.2.1.4 Recruitment of Focus Group Participants and the Consent Process

Three focus group discussions were conducted: one with Motherisk staff, one with Motherisk users, and one with women of child-bearing age. The recruitment strategies for each group are described below. These three groups were selected in order to provide a cross-section of opinions with varying degrees of experience with TIS and physician services. Motherisk staff may offer their own personal perceptions as well as relay the comments of patients they have counseled. Motherisk users may have unique experiences of the service value. Similarly, women who have not used Motherisk may offer more insight into the benefits of physician services, or into attributes that are not intrinsic to either TIS or physician care. Using three focus groups helped to elicit views from a broader representation of the target user population.

The focus group discussion with Motherisk staff was conducted during the working day. Motherisk users were recruited from the general Motherisk line over a two day period. After counseling, callers whose calls had been completed (i.e. were not booked to attend the clinic for a follow-up appointment) were asked if they would like to volunteer to participate in the focus group and were contacted by the research coordinator (RH) if they agreed. The non-users were recruited from an ongoing study on folate supplementation that required them to visit Sick Kids regularly for 30 weeks. The research coordinator for that study asked participants if they would be interested in participating in a focus group discussion. Those who were interested were contacted by RH. A \$20 gift certificate to Chapters book stores was provided to all focus group

participants (except for the Motherisk counselors, who participated during their paid working hours). Refreshments were provided for the discussion (i.e. drinks, light snacks). A summary of focus group participants and dates is presented in Table 9.

**Table 9: Focus Group Details**

<b>Participants</b>	<b>n</b>	<b>Mean Age</b>	<b>Session Date</b>
Motherisk Counselors	5 women	33 (missing 2 values)	Nov. 13, 2007
Women of Child-Bearing Age	2 women	40	Dec. 20, 2007
Motherisk Callers	4 women, 1 man	35	Jan. 31, 2008

All focus group participants were asked to complete two consent forms: one regarding participation and one regarding audio-taping the discussion (provided in Appendix 5 and 6). The focus groups consisted of 2-5 participants. There is no formal method for calculating sample sizes for focus groups, as sample size should be informed by the specific research objectives and may vary from study to study [254]. In general, a size of 3-7 participants is considered appropriate [254]. It has been suggested that three to four groups are generally required to reach the point of saturation [253].

### 3.2.1.5 Focus Group Discussions and Activities

The focus group discussions were facilitated by RH. Each discussion took approximately one hour. The format was an open-ended discussion. The question guide used to facilitate the focus group discussions is provided in Appendix 7. The focus group participants were asked what they think are the values and benefits of TIS and physician care, what framing questions would be most appropriate in reflecting these values and benefits (i.e. is exposure to an anti-depressant an appropriate choice for evaluation), what attributes are most important and what levels and ranges of levels are reasonable, with particular attention paid to the issue of WTP. Participants were asked what they would be willing to pay for a consultation if the government or insurance did not cover it, and if they would be able to assess this cost without also considering work-related costs (e.g., time lost from work, vacation or sick leave) and transportation costs (i.e., parking, gas, and/or public transportation fares). The questions regarding WTP were not intended to generate usable estimates but only to identify plausible ranges of levels for the DCE.

Discussion was initiated with the open-ended question “What are some features you feel are important when asking questions about using medications during pregnancy?” Following the

open discussion, participants were presented with the previously defined attributes and were asked about their appropriateness based on their own experiences, thoughts, and observations. The first focus group was presented with an attribute rating sheet of six potential attributes, including the five initially defined attributes (person you contact, method of contact, time you wait to receive information, cost to you, and helpfulness of advice provided) and cost. After the first focus group discussion, additional potential attributes were added to the attribute rating sheet. New attributes were also added after the second focus group session as they emerged from the discussion. Participants were asked to rate each attribute's importance on a scale from 0 to 10. The attribute rating form is presented in Appendix 8.

### 3.2.1.6 Focus Group Analysis

A formal evaluation of the focus groups was not performed (e.g. grounded theory analysis). Rather, transcripts of the discussions were read by the study coordinator (RH) and examined for recurrent themes. When a point was made that was highly supported by other group members, or appeared to be relevant, it was coded in a particular highlight colour representing a theme. Eight common themes emerged from the discussions, coded as Trust, Convenience, Specialization, Training, Cost, Compassion, Integration with other services, and Types of questions. All three focus groups emphasized that the accuracy of information provided is very important, as is speaking with someone who is highly specialized in this area (Specialization and Training themes). Participants stated repeatedly that they did not mind if the information came to them from a physician or another health care professional as long as they had adequate training (Training). Other important features were speaking with someone who is empathetic, calm and doesn't rush you (Compassion). The idea of anonymity had two dimensions: on one hand, people wanted to speak with someone who had knowledge of their medical history. On the other hand, people appreciated the anonymity provided by the telephone and felt that this allowed them to ask "silly" questions that might otherwise be embarrassing (Trust). The immediacy of asking a question at a telephone-based teratogen service as opposed to going to a doctor's office was seen as an important benefit; the difficulty of obtaining an appointment with a doctor was emphasized (Convenience).

The results of the zero to ten ratings of the attributes are presented in Table 10. The groups were too small to make statistical comparisons between them. Overall, the scores appeared similar,

however it was noted that the women of child-bearing age group gave IP's knowledge of your personal medical history a median rating of 9.5 whereas the Motherisk caller group gave that attribute a median rating of 7. This attribute was not evaluated by the Motherisk counselors.

**Table 10: Attribute Rating by Focus Group Participants**

Attribute	Mean Score*	SD	n
Helpfulness	9.9	0.3	12
Trust in IP (Information Provider)	9.6	0.8	7
Education of IP	9.4	0.8	7
Specialization of IP	9.0	1.8	7
Able to provide specific research study data on topic of interest	8.6	2.1	5
Time available for consultation	8.0	0.6	7
Ease of follow up	7.9	1.5	7
Waiting time for counseling	7.8	2.0	12
IP's knowledge of your personal medical history	7.6	1.7	7
Cost (willingness-to-pay)	6.8	2.2	12
Person (physician vs. other)	6.8	2.4	12
Method (face-to-face vs. telephone)	5.5	2.7	12

\*On a scale from zero to ten (0=least important, 10=most important).

Extensive attention was paid to the WTP ranges suggested by participants (Cost) and to the framing of this attribute, given that Ontarians do not generally pay at the point of care. WTP ranges were extracted from the transcripts and are summarized in Table 11.

**Table 11: Willingness-to-Pay Ranges from Focus Groups**

Inter Quartile Range	Willingness-to-Pay (CDN \$)
Minimum	10
25 <sup>th</sup> percentile	22
Median	40
75 <sup>th</sup> percentile	63
Maximum	100

The WTP ranges were in keeping with costs of telephone consultations available in the U.S. One physician bills from US\$15 to \$22 for five minute increments [255]. TelaDoc, a Dallas-based company that offers medical consultations by telephone, charges US\$35 per call plus a nominal monthly membership fee [256]. Doctor on Call is another U.S.-based service, mainly paid for by employee health plans, and costs \$10 per month for an uninsured family [257]. Another reference quoted a price for physician telephone consults of US\$50 [258]. A summary of the previous DCEs of women's health that have incorporated WTP is presented in Table 12. In these

studies, women were willing to pay to avoid complications, pain, to reduce waiting/treatment time, and to see a sensitive staff member. These studies took place in the UK and Australia, so these ranges may not be applicable to North American settings.

**Table 12: Literature Review of Willingness-to-Pay for Attributes of Women’s Health Services**

Reference	Topic	Attribute	WTP (£)	WTP (US\$)*
Ryan 1997 [214]	Miscarriage management	Avoid complication	492	974
		Reduce pain	231	457
		Reduce time in hospital	125	248
Ryan 1999 [169]	In-vitro fertilization	Seen by staff with positive attitude	1227	2430
San Miguel 2000 [215]	Menorrhagia treatment	1% reduction in complication chance	132	261
Taylor 2003 [219]	Vaginal gel for labour induction	1 hour reduction in time from induction to delivery	25	55 (ASD)**
		1% reduction in epidural chance	9	20 (ASD)**
		1% reduction in cesarean section chance	41	90 (ASD)**
Ryan 2005 [221]	Pre-natal diagnostic testing	1 day reduction in wait time for results	18	36
Wordsworth 2006 [225]	Cervical cancer screening	1% reduction in chance of recall due to inadequate sample	5	10
		1 week reduction in wait time for results	10	20
		1% reduction in chance of dying from cervical cancer	51	101
Seston 2007 [227]	Provision of emergency contraception	Seen by sympathetic & non-judgmental staff	25	50
		Seen privately	20	40
*Exchange rate of £1=\$1.98 was used.				
**Australian Dollar; exchange rate of \$1 ASD = £0.461 was used				

### 3.2.1.7 Final Selection of Attributes and Levels for the Pilot Study

Attributes and levels were selected based on the identified themes in the focus group discussions, the literature review findings, the numerical ratings of attributes and WTP ranges provided by focus group participants. Table 13 provides the attributes and levels used in the pilot survey.

**Table 13: Attributes and Levels Used in the Pilot Survey**

<i>Attribute</i>	<i>Level 1</i>	<i>Level 2</i>
<b>Training of the information provider</b>	Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
<b>Method of contact and waiting time</b>	Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
<b>Knowing the information provider</b>	You have had contact with the information provider before and they will know your medical history	You have never had contact with the information provider before
<b>Trust in skills of the information provider</b>	You have trust in the skills of the information provider	You know nothing about the skills of the information provider
<b>Helpfulness of information</b>	Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
<b>Cost</b>	Level 1: \$10, Level 2: \$50, Level 3: \$90	

Most of these attributes were similar to those pre-selected for testing in focus groups, however the “knowing the information provider” was one that emerged as important through discussion and examination of the literature (Trust). Trust was the most highly valued attribute in a study of preferences for non-health attributes of the GP experience [259]. Another study found that patients were willing to wait longer to see a medical practitioner familiar with their case [240]. A theme from the focus group that was not carried forward was Integration with other services. What the focus group participants were saying in relation to this theme was that counseling by TIS would be improved by a better feedback loop between the TIS, physicians and pharmacists, and that they would like their consultation with Motherisk to become part of their medical record so that their medical team was aware of the advice they had received. While this is an important piece of information of which to be aware, it is perhaps not as relevant to the program evaluation as the other attributes and would be difficult to express as an attribute. Sharing of medical records is an important part of care that could overall be strengthened in Canada, and hopefully improvements in digitization of records will help to remedy this problem. This attribute was mainly raised in the focus group discussion with Motherisk users which was the last one held, so it was not included in the attribute rating form.

### 3.2.1.8 Other Issues in the Design of the Survey Instrument

#### 3.2.1.8.1 Framing the Survey Question

Respondents were asked to imagine that they are a newly pregnant woman (or partner of a newly pregnant woman) who would like more information about using an anti-depressant during the pregnancy. The use of anti-depressants during pregnancy remains controversial [196]. Their appropriateness for use during pregnancy is debated both in the media and the scientific community [260, 261]. In the focus group discussions, Motherisk staff suggested that it is a “mid-level” inquiry in that it is not completely innocuous, yet is not believed to be teratogenic. It is also a common question; 12% of calls to Motherisk are regarding anti-depressants [159]. In a large U.S. cohort, 13% of pregnancies were exposed to anti-depressants [262]. A review of calls to the Australian TIS found that 9% were regarding psychotropic medications [263]. It has been found that women have higher levels of risk perception for psychological medications compared to other types of medications (e.g. gastric drugs and antibiotics) [159]. This framing question is intended to establish preferences for counseling when the exposure is controversial, and the decision to use the medication may be complex and multifactorial.

#### 3.2.1.8.2 Demographic Questions

Basic demographic questions, similar to those included in census taking, were also included after the choice questions (e.g. gender, age, income, education, and employment status). Other questions were included that were hypothesized to have an impact on a person’s perspective on teratology counseling, such as whether the respondent has children, have any children with a birth defect, have used the Motherisk Program, have a family doctor, and have experience with anti-depressants. Questions considered to be of a more sensitive nature (e.g. income) were placed later in the questionnaire (see Appendix 11 for the full questionnaire).

### 3.2.2 Selection of Experimental Design

#### 3.2.2.1 Creating Optimal Choice Sets

The survey had a fixed design, meaning that the choice sets were the same in each survey version (as opposed to an adaptive design, which is performed on a computer using specialized software that designs an individual survey for each respondent and adapts future survey questions to the respondent’s previous answers). As this survey was offered both on paper and online in order to

avoid excluding non-computer users, the adaptive method was not an option. A blocked design was used, that is, multiple versions of the survey were generated with subsets of questions presented in each version. For example, if sixty questions are generated, version A contains 1-20, version B contains 21-40, etc. A blocked design helps to control for contextual bias and ordering effects as different respondents are answering different sets of questions. A further discussion of design efficiency is presented in section 3.2.2.4.

Previous studies have found that the ordering of attributes has little effect on utility weights [264], and that the ordering of choice sets within the survey does not have an effect on responses [167]. One study did find that respondents were more sensitive to price when it was presented last as opposed to first [265]. Based on these findings and in the interest of preserving simplicity, it was decided that question order would not be varied. Each version of the survey was identical except for the levels within the choice pairs, that is, they had the same number of choice pairs, and the pre-amble, instructions, and the fixed choice pairs were the same.

The proposed survey had a discrete binary choice format, meaning that respondents were asked to select their preferred service scenario from two possible scenarios. Presenting respondents with a discrete choice rather than ranking or rating may better reflect real life choices and has become a preferred method in health care assessments [213]. Real life choices may be multiple, for example we don't just choose if we want chocolate or vanilla ice cream, but we can choose from up to 34 flavours. Some surveys therefore include more than two potential options. This increases the complexity of the survey, and while this may provide data about preferences more efficiently, in the interest of simplicity, only two choices were presented in this study. As well, as many attributes ultimately only had two levels, it would be difficult to avoid level overlap between options if three or more options were presented. Asking respondents to rate their choice provides information regarding strength of preference as well as direction [266]. However, an advantage of offering a discrete choice rather than rating is that interactions between attributes can be measured in addition to main effects [266]. The survey used a full profile design rather than partial, meaning that all attributes were presented in each choice task rather than a selection of attributes.

### 3.2.2.2 Allowing for Non-Demanders with a “None” or “Opt out” Option

Some surveys offer respondents a “none” option simultaneously (i.e. to choose neither of the options). This may lead to loss of data if many respondents choose to exercise this option.

Alternatively, some researchers have offered respondents an “opt out” option, where they follow up the forced choice with a statement such as “Would you actually use your selection in real life, or would you do nothing?” These types of questions have been referred to as an opt out or “dual response none option”. There are advantages and disadvantages to providing an opt out option.

These are summarized in Table 14.

**Table 14: Advantages of Offering Opt Out/None Option**

<b>Disadvantages of Opt Out/ None Option</b>	<b>Advantages of Opt Out/ None Option</b>
Increased respondent burden	More accurate reflection of real life choices
Lack of information on implications of opt out response – what is the respondent choosing when they choose nothing?	More accurate estimate of WTP

It has been argued that offering a none or opt out option provides a better reflection of real life behaviour. Not allowing participants to opt out of their choice or choose neither forces all respondents to be demanders of the good or service being evaluated, although some may be non-demanders. Depending on the question, it is possible that respondents are selecting only their most preferred scenario rather than one they would actually use [267, 268]. By not taking real life behaviour into account, preferences for attributes may be over-estimated, as coefficients in the regression model are based on how many times a particular level was selected. Providing a none or opt out option reduces the number of times a level can be selected. Over-estimation of preferences is of particular importance when WTP is estimated. Including a none option in the DCE may also increase design efficiency [269].

There are also, however, disadvantages to providing a none or opt out option. Both would increase the amount of time to complete the survey. Adding to respondent burden may reduce response rates, as well as attention given to the survey overall. If given a none option, respondents may choose to use it rather than make a difficult choice (although this is not a problem when an opt out is used) [267]. Most importantly, it is important to understand what the respondent is indicating when they elect to use the none option or opt out, that is, to be a non-demander [267]. If the none or opt out option is undefined, it remains unclear whether people are

choosing to do nothing or stick with their current good/service. Some surveys may define the none or opt out as “stick with my current health care provider”, for example (and determine who that is in another segment of the survey), whereas others might leave it as “I would not choose either of these options.” What the non-demander is choosing may be readily quantifiable. For example, in a study on cervical cancer screening, it could be assumed that when choosing a “neither” screening option, respondents are choosing to do nothing and accept a higher risk of cervical cancer. Without specifying this, however, it may be unclear to respondents and this will have implications to how the modeling is performed [267].

DCEs that have included none or opt options have had them taken up to varying degrees. In a cervical cancer screening study, 27 women out of 491 surveyed (6%) took advantage of a “no screening” option. Eleven of these women always chose no screening (2%), while 16 chose it on one occasion. This resulted in “no screening” being chosen in 3.4% of the observations [267]. In a study of services after rape, women were given the option of risking pregnancy rather than choose one of the two services offered and the “neither service” option was chosen by 59% of the sample on at least one occasion [222]. A study of colorectal cancer screening preferences found that 30% of the sample chose “no screening” [270]. It is difficult to predict to what extent this option would be used in the present survey as in previous research it has varied widely.

It is also important to take into account the familiarity a respondent will have with the question at hand [268]. For example, if the DCE was assessing preferences for GP care, this may be an area where the respondent has considerable experience and understanding, but if the survey is regarding an unfamiliar or complex treatment it can't be expected that the respondent will be aware of all the options available and therefore they themselves may be unable to define what opting out means to them.

It was initially decided not to offer a none or opt out option, as it was expected that in real life a person would seek out some form of medical advice in the anti-depressant scenario rather than choose to do nothing. In fact, it is likely that multiple sources of information would be consulted. Midway through data collection it was decided to re-visit this decision due to concerns regarding over-estimation of coefficients and WTP. To inform this decision, consultations with experts in the field and with previous survey participants were undertaken. A convenience sample of eight previous survey participants were contacted and asked about how an opt out option may have

affected their experience completing the survey. Two participants indicated that they might have used an opt out option if it had been available, but the majority did not. It was difficult to get respondents to describe what choosing an opt out would mean to them, adding further support to the notion that as there is no status quo in the field of teratology counseling, the opt out question may create cognitive difficulties. Six researchers who have conducted DCEs were consulted by email. Overall these discussions echoed the findings in the literature, which is that while including an opt out may be a more accurate reflection of real life choices, the difficulties in defining the status quo in this particular context are large, and respondent burden is increased. For these reasons it was decided to continue without including an opt out option. In the demographic section of the survey following the choice tasks, respondents were asked to choose all the information sources they would use in real life; the responses to this question will shed light on whether it is reasonable to expect that there are no non-demanders of information and whether there is a status quo option in this context.

### 3.2.2.3 Sample Size

While there is no gold standard for sample size calculations in CA studies, there is a formula available that has been proposed as a general guideline for calculating sample sizes:  $nta/c \geq 500$ , where  $n$  = number of respondents,  $t$  = number of tasks,  $a$  = number of alternatives per task, and  $c$  is equal to the largest number of levels for any one attribute or the largest product of levels of any two attributes if two-way interactions are to be studied [271]. Rearranging to solve for  $n$  gives:  $n = (500*c) / (t*a)$ . In this study, we planned to ask respondents to complete approximately 12 choice tasks, therefore  $t = 12$ . As the choice for each task is binary,  $a = 2$ . The largest number of levels is 3, therefore  $c = 3 \times 2 = 6$  (to account for two-way interactions). Solving for  $n$  gives:  $(500*6) / (12*2) = 125$ . Estimating a 10% rate of unusable surveys and a 60% rate of return of questionnaires yields a potential target sample size of 200. The efficiencies of various survey designs of different sample sizes in this range were examined using Sawtooth®.

### 3.2.2.4 Survey Design

Six attributes, five with two levels and one with three levels (cost), were ultimately selected for evaluation. While there is no gold standard, it is generally considered that between four and six attributes is appropriate, as more than six may place too great a cognitive burden on the

respondent [272]. This yields 96 potential scenarios ( $3^1 \times 2^5$ ), or 48 choice pairs. It has been shown that up to 20 choice pairs is acceptable before data quality will be degraded by respondent fatigue, therefore presenting all 48 choice pairs is not feasible [273]. A fractional factorial design was therefore used to obtain a manageable number of choice pairs based on the 96 potential scenarios.

Huber & Zwerina [274] identified four principles that need to be satisfied to create an efficient design:

1. *Level balance* (i.e. each level appears approximately the same number of times in each survey version)
2. *Orthogonality* (i.e. there is zero statistical correlation between the attributes)
3. *Minimal overlap* (i.e. the levels in the scenarios in the choice pair are different)
4. *Utility balance* (i.e. the scenarios in the choice pair are expected to have roughly equal probabilities of being selected by the respondent).

Designs that satisfy these conditions are said to have maximum D-efficiency. D-efficiency is a measure of covariance in the design matrix. The design matrix is defined as  $x$  and represents the matrix of attribute levels [275]. The formula for D-efficiency is:

$$\text{D-efficiency} = [|\Omega|^{1/K}]^{-1}$$

Where  $K$  is the number of parameters to estimate, and  $\Omega$  is the covariance matrix of the vector of the parameters [275]. The covariance matrix is defined as:

$$\Omega = \sigma^2(x'x)^{-1}$$

An optimal design will define the design matrix ( $x$ ) in a manner that minimizes the covariance matrix ( $\Omega$ ). In simple terms, efficiency increases as variances decrease [276]. Other measures of efficiency exist, however D-efficiency is the most commonly used measure in the field as it is less computationally burdensome [275].

Different methods are available for selecting optimal survey designs. Design strategies often employ an orthogonal main effects plan (OMEPE) to determine scenario design, which allows for the estimation of uncorrelated main effects, assuming that two- and three-way interactions between attributes are negligible [277]. To determine the smallest usable OMEPE, the  $L^{MA}$  factorial approach may be employed. The  $L^{MA}$  factorial requires the researcher to input their  $L$  (number of levels),  $M$  (total number of generic choice outcomes) and  $A$  (number of attributes) [165]. For example, in this study there are two choice outcomes ( $M=2$ ), six attributes ( $A=6$ ) and most of the attributes have two levels ( $L=2$ ). The collective factorial is therefore  $2^{2 \times 6}$  or  $2^{12}$ . The smallest OMEPE is then determined by summing the separate degrees of freedom in each main effect [165]. Each main effect has  $L-1$  degrees of freedom, (1 in this example), and there are 12 main effects, hence there is a total of 12 degrees of freedom. The smallest OMEPE associated with this design would be 16 choice sets, according to commonly used factorial tables [165]. It can be seen even in this example, that designing surveys using the  $L^{MA}$  factorial to determine the smallest OMEPE becomes difficult when attributes have different numbers of levels and the numbers of levels are odd. Also, information regarding the pairing of scenarios into binary tasks is not available. Another option is to use a pre-existing design catalogue orthogonal array, however these designs often require modification which will reduce efficiency [276]. Some statistical software packages can also be used to design an OMEPE, including SAS® and SPEED®. Designing choice sets is also more complex if two-way interactions between attributes are to be measured as well as main effects.

Further design strategies are needed in order to efficiently pair scenarios into binary choice tasks. Some of these design strategies are outlined by Street et al [277]. Street advocates first creating a set of scenarios that satisfy the orthogonality conditions (i.e. the smallest OMEPE), and then using a fold over technique to create the scenario pair (i.e. if there are two levels, 0 and 1, and 0 is the level used in the initial scenario, 1 is the level used in the fold over). With the fold over technique, each scenario initially defined will have a mirror image scenario as its choice pair. This technique also becomes difficult, however, if an attribute has more than two levels. In the past, researchers have randomly paired scenarios [278, 279] however this approach has several drawbacks, principally that the efficient design principles of utility balance and level overlap may be violated. While determining an OMEPE can be readily achieved, survey design becomes

more difficult when attributes contain different number of levels, scenarios need to be paired into efficient choice pairs, and if estimation of two-way interactions is desired.

Sawtooth® software creates survey designs with paired scenarios and tests the efficiency of these designs [280]. By manipulating different survey parameters (number of versions, the number of respondents, and the number of discrete choice tasks (choice pairs) presented to the respondent), Sawtooth® was used to estimate the D-efficiency of various designs using the complete enumeration strategy, which generates designs that conform to the principles of orthogonality, minimal overlap, and level balance.

Some of the decisions regarding survey design are subjective. For example, the researcher may want to select a design with fewer choice pairs if respondent fatigue is a concern. However, in a study where respondents are expected to be highly dedicated and could be expected to handle a longer survey instrument, a survey design with more choice pairs may be selected. Similarly, the researcher may want a smaller or larger number of respondents depending on recruitment and feasibility issues. How many times a level appears in the version should also be considered when selecting the survey design to satisfy the principle of level balance. Finally, no design can achieve perfect efficiency unless a full factorial design is used (i.e. all potential scenarios are presented to the respondent). Therefore the relative efficiency of different designs should be examined.

During survey design, the number of respondents was varied from 150-250, as this range of respondents would be feasible and affordable to obtain, and was informed by the rough sample size calculation. The number of versions was varied between three and four. A higher number of versions would increase efficiency; however the number of versions must be kept low so as to be logistically manageable, especially as the survey is offered to respondents both online and on paper. During survey design, the number of choice pairs per version was varied from 10-14. Three fixed choice pairs would be added to each version, therefore totals of 13-17 choice pairs were considered. It was assumed that respondents could handle up to 20 choice tasks before the quality of the responses would begin to degrade [273]. A greater number of choice pairs would increase efficiency, however respondent fatigue must be considered.

After reviewing the relative efficiencies and level frequencies (the difference between the maximum number of times and the minimum number of times a level appears) of several

potential survey designs, the research team selected a survey design that had three versions, required 200 respondents, and had 12 choice pairs. This design had high D-efficiency relative to the other potential designs and was also logistically feasible. As mentioned in the previous paragraph, three fixed choice pairs were added to each version (also refer to the consistency tests described below). Each version therefore contained a total of 15 choice pairs. The survey was designed to estimate main effects; the design strategy (complete enumeration with minimal overlap) and sample size were not set to estimate two-way interactions. This is a potential limitation of the design because if interactions exist, they will affect the beta estimates. Exploratory analysis of interactions was conducted in Sawtooth® where possible (see section 3.3.3.2).

### 3.2.2.5 Consistency Tests

Three fixed choice tasks were included in the survey as tests of consistency. A best/worst task was designed to test if respondents were choosing logically: scenario A had levels that were objectively superior (e.g. cost was \$10), while scenario had B levels that were objectively inferior (e.g. cost was \$90) (refer to Appendix 11 for the full survey). For the levels that were subjective (training of information provider and method of contact), both scenarios contained the same levels (family doctor was used for information provider training and appointment was used for method of contact). The best/worst task appeared as question number four and was repeated as question number twelve. A description of how people who failed the best/worst task were assessed and handled is provided in Section 3.2.5.4.

Another fixed choice task was included to assess the predictive accuracy of the model and to provide further evidence as to preferences for TIS versus family physician. Scenario A had levels that best represented a TIS, while scenario B had levels that best represented a family doctor visit. The responses to this fixed task will be compared to the utility derived from the regression model for these two scenarios.

### 3.2.3 Pilot Testing of the Survey Instrument

The pilot study had five objectives: i) to assess feasibility of recruitment; ii) to assess ease of completion of the survey instrument; iii) to assess willingness to trade between attributes; iv) to

assess directionality of preferences for attribute levels and v) to assess the ordering of preference magnitudes for logic.

Recruitment occurred over a period of two weeks in August, 2008. Two ads were placed in the Metro Newspaper, provided for free on the Toronto Transit System. Twenty-five volunteers contacted the research coordinator and were mailed the survey package; 21 surveys were returned (15 women and 6 men). Participant's average age was 36 years (SD 9.9). The sample was mainly Caucasian (14/21), with five describing themselves as Asian, one as African, and one as other. The majority (90%) had at least some college/university education, and 24% had post-graduate education. Eight had high household incomes (over \$80,000 gross household per year), six had medium (\$40,000-79,999), five had low incomes (\$0-39,999) and two preferred to not provide this information. Approximately half (57%) were employed, while 24% were students or full time home-makers.

Fixed task responses showed logical and consistent decision making. A multinomial logit regression analysis of the choice data was conducted using the Sawtooth SMRT® program. The Sawtooth program uses effects coding. The practical implication of this is that the utilities reported sum to zero. The SAS analysis, which was used for the results of the main study, used dummy coding (see Section 3.2.5.7). To facilitate comparisons between the Sawtooth results and the SAS results, the Sawtooth results were presented as though dummy coding had been performed, which means that the reference level has zero utility. Effects coding and dummy coding differ in how they label predictor variables. In effects coding, only ones, zeros, and minus ones are used to describe to what group the data belongs, and the reference level is always set to minus one [281]. In dummy coding, only zeros and ones are generally used to describe group membership. There are not substantive differences between coding methods for simple regression analysis, but effects coding may be better when interactions are being estimated.

Analysis of the choice data revealed that some respondents demonstrated unwillingness to trade on certain attribute levels. They were: obtaining very helpful information (two respondents), having a family doctor as the information provider (IP) (two), and having trust in the skills of the IP (one). Most respondents, however, were willing to trade and trade-offs between attributes was observed (see Table 15).

The regression analysis showed that statistically significant attributes influencing the choice of service were helpfulness of information, trust in the skills of the IP, and knowing the IP (see Table 15) (p-value greater than 0.05 was considered to be statistically significant). In terms of the directionality of preference, some of the levels are subjective and therefore *a priori* expectations with respect to the sign of the beta estimate were not made. For attribute levels where there was an objective directionality that was expected *a priori*, the coefficient signs were in the expected directions (specifically, being unaware of the IP's skills was negative, receiving somewhat helpful information was negative, and higher costs were negative).

The marginal utility of money was calculated by obtaining the slope of the cost attribute levels (the x-axis points were \$10, \$50, \$90; the corresponding y-axis points were 0, -0.6255, -0.8061. See Table 26 for further details). Marginal rates of substitution were calculated to estimate WTP by dividing each beta estimate by the marginal utility of money. Participants were willing to pay \$111 to obtain information that was very helpful compared to somewhat helpful, and \$98 to have trust in the skills of the IP rather than knowing nothing about them.

**Table 15: Results of Multinomial Logit Regression Analysis of Pilot Choice Data (n=21)**

Attributes	Levels	Beta Estimate*	WTP (\$)	P
Type of training of IP	Counselor with specialized training	-		0.077
	Family doctor	0.338	33	
Counseling method & wait time	Make appointment	-		0.080
	Call telephone service	0.350	35	
Knowing the IP	You have met the IP before & they know your medical history	-	52	0.005
	The IP is not known to you	-0.526		
Trust in the skills of the IP	You have trust in the IP's skills	-	98	<.001
	You are unaware of the IP's skills	-0.986		
Helpfulness of Information	Enough information	-	111	<.001
	Some information	-1.121		
Cost to you	\$10	-	Slope= 0.0101	
	\$50	-0.626		0.021
	\$90	-0.806		0.001

\*(-) represents the reference level

Fourteen respondents were de-briefed in interviews following survey completion. De-briefing revealed that the survey was overall considered to be understandable and easy to complete.

Interviewees were comfortable with the cost attribute even though most health services in Canada are public. Reported completion times were 15 to 60 minutes.

Based on the recruitment and survey completion rates, it was determined that recruitment was feasible and the survey instrument was easy to complete. The preferred attributes were consistent with *a priori* expectations. Based on these findings, it was concluded that the survey was robust. However, some modifications were made. First, the wording of the attribute related to trust in the IP was changed. It was thought that the word “trust” may elicit emotions and subjectivity that were not intended. The reason for including this attribute was to assess the importance of factors like reputation. Therefore the wording was changed to “you have confidence in the skills of the IP” Second, the wording of the “knowing the IP” attribute was slightly altered from “you have had contact with the IP before and they will know your medical history” to “you have met the IP before and they know your medical history” to make it more clear. Finally, some of the demographic questions were moved to the beginning of the survey. This was thought to be important for online respondents, so that if they only partly completed the survey, some initial demographic information about the respondent would be available. The demographic questions that were moved to the front were gender, age, and postal code. Recruitment for the main study then began. Table 16 shows an example of a discrete choice task used in the final survey.

**Table 16: Sample Question from Final Survey**

**You can use one of two health services to get more information about using your anti-depressant while you are pregnant.**

**1. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
The information provider is not known to you	You have met the information provider before and they know your medical history
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$90	\$50

Check ONE box only:



### 3.2.4 Measurement of Preferences

#### 3.2.4.1 Recruitment Strategy

The goal was to achieve a sample that included a variety of backgrounds with regards to socio-economic status, age, ethnicity, experience with pregnancy, and experience with anti-depressant use. Subjects were recruited from the general community using three approaches to recruitment: newspaper advertising, online postings, and neighbourhood community flyer postings.

##### 3.2.4.1.1 Newspaper Advertising

Advertisements were placed in free commuter papers such as the Metro Newspaper, and other free community papers such as the North York Guardian. The Metro claims that 53% of its readers do not read any other newspaper, that there are 950,000 daily readers in Canada, that it has an equal number of male and female readers, and that 70% of its readers are under the age of 45 [282]. Previous studies have found newspaper advertisements to be an effective recruiting

method. An advertisement for participants for a healthy eating behaviours study placed in a newspaper for five days with a daily readership of 75,000 resulted in 282 eligible respondents [283]. A comparison of several different recruitment strategies for a smoking cessation study found that of multiple paid newspaper advertisements, free media (i.e., television and radio), referrals, Health Management Organization (HMO) newsletters, targeted mailings, face-to-face, and passive recruitment, the most reliable and affordable channel was paid newspaper advertisements [284]. Another study that compared newspaper advertising, radio advertising, approaches to community groups, approaches via general practices, and an electoral roll mail-out for recruitment into a longitudinal intervention study in Australia found that newspaper advertising and electoral roll mail-out were the most efficient methods of recruitment in terms of absolute numbers of participants recruited and cost per participant [285]. Subjects recruited into a chronic shoulder pain study by their GPs or by newspaper advertisement were not different with respect to demographic characteristics and clinical outcome measures at baseline [286].

#### 3.2.4.1.2 Online Community Postings

Advertisements were placed on online community sites such as craigslist.ca and kijiji.ca, which are intended as community websites for use by diverse groups. Postings were placed in general categories. Small fees were sometimes paid to raise the postings to a prominent position of on the web page.

#### 3.2.4.1.3 Neighbourhood Community Postings

Advertisement flyers were placed on free message boards in community centres and in main buildings on the University of Toronto campus.

#### 3.2.4.2 Consent and Follow-Up Process

The advertisement stated that the Hospital for Sick Children was looking for people to complete a survey on their preferences for counseling services on medication use during pregnancy, and that adults between 18 and 65 years old of all backgrounds were eligible (refer to Appendix 9 for an example of the recruitment advertisement). The office telephone number and email address for the study coordinator (RH) was provided. Individuals who contacted RH received a more detailed description of the study. If individuals agreed to participate, they were offered the choice of completing the survey on paper or online. Paper-based respondents were mailed a study

package containing an explanatory letter in lieu of a consent form, the survey, and an addressed, stamped envelope for returning the completed survey to RH. The explanatory letter addressed the issues normally included in a consent form (i.e. purpose of the study, rights of study participants, confidentiality, time to complete the survey, etc.), and explained that consent was inferred from the completion and return of the survey. Online respondents were also mailed the consent letter and a user name to access the secure survey website. The internet offers a great opportunity for researchers to collect data quickly, to save time on data entry, and to reduce data entry errors. Only offering an online survey, however, may exclude members of society who do not own or use computers. A cross-section of society was desired for this study which is why the survey was offered to respondents in two possible forms (online and on paper by mail). Demographic characteristics of the online and paper respondents were compared (see Table 22).

Three weeks after the first mailing, volunteers who had not yet completed the survey were telephoned with a follow-up reminder. A second reminder call was made three weeks later. After two reminder calls, the non-respondent was considered lost to follow-up. Telephone reminders have been found to be both an effective and inexpensive method of increasing responses to mailed surveys [287]. The survey was designed in accordance with the survey design principles and guidelines outlined by Dillman [288]. A \$2 gift certificate to Tim Horton's was provided in the package. The inclusion of even a small financial incentive or gift has been shown to increase response rates [288, 289].

### 3.2.5 Data Management and Analysis

#### 3.2.5.1 Preparation of the Database

There were two survey data sources: online responses and paper responses. Data management procedures for each source are described individually.

##### 3.2.5.1.1 Online responses

Sawtooth Software® was contracted to host and maintain the website [www.preferencestudy.com](http://www.preferencestudy.com). Data from the website were downloaded into the Sawtooth Software® SMRT program (hereafter referred to as SMRT), which was used for the first phase of data analysis. The responses were automatically sorted into the categories of complete,

incomplete, and not started. When the data were downloaded from the website they were automatically stored as a Microsoft Excel® .csv file.

### **3.2.5.1.2 Paper responses**

Paper responses were entered by hand into a .csv file, and imported into SMRT using the “Accumulate Paper & Pencil Data” wizard. Data entered by hand was double-checked by RH. The two .csv files (online and paper respondents) were merged into one file for importation into SAS Version 9.2. Demographic and choice data were stored in separate files as they were formatted differently and then merged using SAS commands.

### **3.2.5.2 Preliminary Analyses**

#### **3.2.5.2.1 Incomplete data**

Respondents who provided incomplete data were compared to those who provided complete data with respect to the demographic variables available. An incomplete respondent was defined as someone who answered fewer than 8 of the choice tasks (i.e. less than half).

#### **3.2.5.2.2 Comparisons of Demographic Variables**

The gender of those who consented and completed the study was compared to those who consented but did not complete the study, as this was the only demographic variable known for non-completers. Demographic variables for online and paper respondents were compared using appropriate chi-square and t-tests.

#### **3.2.5.3 Descriptive Statistics for Demographic Variables**

Descriptive analyses of demographic variables were conducted in SAS using PROC FREQ and PROC MEANS. The demographic data were thoroughly examined prior to the regression analysis. Means and standard deviations for age for the sample and for males and females were determined. Decisions were made about handling the age variable as a categorical or continuous variable in the regression model based on its distribution.

Frequencies were examined for the categorical responses to gender, education, income, language, ethnicity, and employment status, both for the group overall and for the male and female sub-groups. Based on the distributions across the categories, decisions were made

regarding combining responses so that there were enough responses in each category to conduct meaningful analyses.

The number of responses to the questions “are you currently taking anti-depressants?”, “are you or your partner currently pregnant”, “have you had any children with a birth defect?”, and “do you have any close friends or relatives who have had a child with a birth defect” were examined to determine if there were enough responses to conduct meaningful categorical analyses. Other categorical responses were feeling anxious about the pregnancy, experience with Motherisk, having a family doctor, having children, and being born in Canada.

#### **3.2.5.4 Identification of Lexicographic and Illogical Decision Makers**

Respondents who always chose based on one level were identified (termed lexicographic respondents or unwilling to trade). Respondents who responded illogically and inconsistently to the fixed choice tasks were identified (that is, those who chose the worst case scenario over the best case scenario). Decisions were made about how to handle such respondents based on how many existed and what impact, if any, they had on the regression model. The regression model was run with and without the lexicographic, illogical and inconsistent decision makers.

Differences between the models were examined based on coefficient signs and differences in the coefficients using the likelihood ratio test. If there were significant differences between the models, further analysis would be required. If there were not significant differences, all respondents would be retained in the final model.

#### **3.2.5.5 Regression Modeling**

Discrete choice data can be analyzed using different regression models. The most commonly used regression models are logit, mixed logit, and probit [290, 291]. A linear model is unsuitable as they are used to estimate continuous outcome variables; a choice outcome is dichotomous therefore a logit or probit model is required. The logit and probit models mainly differ in how they treat error and unobserved factors [290]. Although the different models may not lead to substantively different results, a rationale for using the logit model is provided.

**Table 17: Properties, Advantages, and Disadvantages of Potential Discrete Choice Regression Models**

<b>Model</b>	<b>Assumption Regarding Unobserved Factors</b>	<b>Advantages</b>	<b>Disadvantages</b>
Logit	Unobserved factors are uncorrelated over alternatives; follow extreme value distribution	Choice probability takes closed form which facilitates interpretation; widely used	Assumption of no correlation may be inappropriate
Mixed Logit	Allows the unobserved factors to follow any distribution	Allows for heterogeneity and homogeneity between and within individuals	Not fully functional in SAS
Probit	Unobserved factors are distributed jointly normal	Can handle correlations over alternatives and time	Relies on the normal distribution which may be inappropriate

Logit is the most often used discrete choice model. However, the assumption that there is no correlation between unobserved factors may be inappropriate. To use a common example, perhaps a person dislikes bus travel because they dislike crowds. For the same reason they may also dislike rail travel; therefore the unobserved factors affecting choice are related [290]. As well, dislike of crowds may persist over time, so that repeated questions over time may have a correlation of unobserved factors [290]. To avoid this assumption of unobserved factors being independent, a probit model may be used, which assumes that the unobserved factors have a normal distribution. This assumption may also be invalid in certain situations [290]. A drawback to the use of probit models is that due to the nature of the probability function (i.e. that it is not constrained between zero and one), the model estimates can't be used to predict the probabilities of choice of different scenarios, which is often an important part of determining the health policy implications of discrete choice surveys [270]. Generally, it is not thought that major substantive differences arise between probit and logit analyses [292].

Mixed logit allows the unobserved factors to follow any distribution, which makes it an attractive potential choice of model [290]. There are practical reasons for not using it at this point, however, as SAS currently does not have functionality for analyzing mixed logit discrete choice models with repeated choices made by the same individual. To analyze a discrete choice survey of the design used here (that is, each individual contributes 12 choice observations) in the current SAS version, each observation would have to be coded as belonging to a separate individual which results in the sacrifice of important data. Once the SAS program is able to

analyse the choice data allowing for multiple observations from the same individual, this model may be preferable over logit and probit due to the more flexible distribution assumption for the unobserved factors.

Modeling of discrete choice data is more complicated if more than two options are provided. If a person is asked to choose from multiple options rather than rank or rate the options, data are lost as to the order of preferences for the unselected options. Multinomial or conditional logit models may violate the axiom of Independence of Irrelevant Alternatives (IIA), rendering their estimates invalid. IIA implies that the addition of further alternatives should not affect the probability of the preferred alternative being chosen. This is commonly illustrated using the “red bus, blue bus” example [293]. In this example, respondents are asked to choose their preferred mode of transport between car and bus. Assume the probability of choosing each alternative is equal, 0.5, and the odds ratio is one. If a third alternative was added, so that the choice is now between car, red bus, and blue bus, presumably the probability of choosing car has not been altered because the red and blue bus alternatives are equally attractive, however in order for the odds of choosing car to be preserved as one, the probabilities need to be 0.33 for each alternative. In essence, violating the IIA axiom may lead to a failure to appropriately assign probabilities to choices, and this violation can be remedied by using more sophisticated models such as nested or mixed logit.

As this discrete choice survey is a simple binary choice, multinomial logit analysis was used. This is the best documented model in the literature and in terms of SAS experience, and the estimates can be used to estimate the probabilities of the utilization of different service scenarios.

### 3.2.5.6 Logit Regression in SMRT to Assess Data

The first multinomial logit regression was conducted in SMRT. SMRT is not able to include demographic interaction variables in the regression analysis. The purpose of the initial regression in SMRT was to assess the magnitude of the attribute coefficients and whether the directions of preferences were in the expected order (for example, having confidence in the skills of the information provider should be preferred over not having confidence). The size of the coefficients was assessed to determine if the most strongly preferred attributes were consistent with *a priori* expectations and the pilot study. Importance of attributes was calculated by summing all the beta estimates and then dividing each attribute’s beta estimate by the total to yield a percent score (i.e. if the total was 2.0 and one level has utility of 0.5, the importance score

is 25). For cost, the only attribute with more than two levels, the importance score was obtained by calculating the absolute value of the difference between the largest and smallest coefficients.

### 3.2.5.7 Multinomial Logit Regression in SAS

Multinomial logit regression was conducted using SAS in order to include demographic interaction variables. SAS has released instructions for analysis of discrete choice experiments using PROC PHREG [294]. A main effects model was first estimated, which replicated the SMRT regression. An interaction model was then estimated.

### 3.2.5.8 Building the Interaction Model

The main effects model contained the six attributes (training, method, knowing, confidence, information, and cost). All demographic variables assessed in the survey were individually tested in the base model, except for those with response frequencies less than five. Demographic variables were added to the base model one at a time and fit assessed with each new variable tested, with variables displaying coefficient p-values greater than 0.2 being rejected from the model. Coefficient variables that displayed significance levels of less than 0.2 were identified and after the identification of all variables significant at this level, they were run together in one model. Variables that displayed  $p < 0.05$  were retained. Models were run repeatedly until only interaction variables that were significant at the 0.05 level remained. As a final step, the joint significance of the variables that were not significant at the 0.2 level was assessed (i.e. a model was run containing all previously rejected variables). This step is important as it helps to identify the confounding variables. Models were evaluated for goodness of fit using the likelihood ratio chi-square statistic for the global test of zero model coefficients and McFadden's pseudo  $R^2$  [270]. The modeling results were expressed as regression coefficients, with corresponding 95% confidence intervals and P-values. To facilitate interpretation of results for demographic interactions of interest, the sample was split according to the demographic characteristic (e.g. male and female) and the base regression models were run for the separate groups and the coefficients and WTP estimates were visually compared. It was thought that the split samples would be of too small of a sample size to conduct meaningful comparisons, but that comparing WTP values for the different groups might be the most interesting way to observe the impact of the interaction. It was hypothesized that many demographic variables would interact with the model, including gender, income, previous experience with Motherisk, and ethnicity.

### 3.2.5.9 Use of Coefficients to Determine Willingness-to-Pay

Using the estimates in the interaction model, the marginal utility of money was calculated by estimating the slope of the line obtained plotting the regression coefficient for cost on the y-axis, against the cost levels on the x-axis (\$10, \$50, \$90). The beta estimates for the service attributes were then divided by the marginal utility of money to calculate WTP. The calculation of the marginal utility of money assumes linearity of this variable. The data were inspected to determine if the relationship was linear. If linearity is not satisfied, appropriate sensitivity analyses need to be conducted.

### 3.2.5.10 Determination of 95% Confidence Intervals for Willingness-to-Pay through Bootstrapping

Confidence limits for the WTP estimates for each attribute were desired. There are a few potential methods for determining confidence limits for WTP data, but at this point there is no gold standard method [295]. Bootstrapping is a method commonly used in economics to generate confidence intervals and other statistics from small datasets; new datasets are generated by randomly sampling with replacement from the original dataset. The new datasets can be used to estimate confidence intervals and standard errors, and in choice data are considered to be robust to noisy data and misspecifications of the model [295]. The SAS system was used to generate 1000 new datasets with 1000 individuals per dataset by sampling with replacement from the original dataset (PROC SURVEYSELECT was used to generate the IDs used in the datasets and PROC SQL was then used to match the generated IDs with the original data). Regressions were run on each of the new datasets as previously described. The marginal utility of money was then calculated in each dataset using the method previously described. WTP was then determined for each dataset. The WTP values were then sorted in ascending order and the 25<sup>th</sup> and 975<sup>th</sup> data points were used as the lower and upper confidence limits respectively for each attribute.

### 3.2.5.11 Use of Coefficients to Assess Utility of Different Scenarios

Level coefficients can be combined to determine the utility of various service scenarios. This is done by adding the utilities for the levels of interest. Scenarios of interest included the ideal scenario (the most preferred levels), the worst scenario (the least preferred levels), TIS (levels that best represent a North American TIS) and family doctor (levels that best represent a family doctor visit). The overall utility of each of these scenarios was evaluated.

### 3.2.5.12 Real Life Use of Information Sources

Respondents were asked to indicate all information sources they expected to consult in real life if they were in the situation of the exposed pregnancy, from a list of nine common sources. These data were analysed using descriptive statistics. Uncontrolled comparisons between real life use of information and demographic characteristics were conducted.

## 3.3 Results

### 3.3.1 Recruitment of Participants

Recruitment occurred between October 21, 2008 and March 8, 2009. The majority of people who contacted the researcher volunteered to take the survey (81%, see Table 18). The majority of volunteers chose to complete the survey online rather than on paper by mail (80% vs. 20%, Table 18). Volunteers were reliable, with 85% completing the survey (completion in this context also including those who only provided partial data), leading to a total sample size of 175. Based on the calculations provided in the methods section, this sample size was adequate. Originally, 125 completed surveys were required; the sample size was set to 200 assuming only 60% would complete the survey, which was a lower rate of completion than what was obtained. A sample size of 200 was confirmed when relative efficiencies of various designs were compared. The relative efficiency of a design with 175 is still favourably high. Male volunteers were less likely to complete the study than female volunteers (75% of male volunteers completed the study compared to 88% of female volunteers; chi-square statistic  $p=0.032$ ).

**Table 18: Recruitment of Participants**

	<b>n</b>	<b>%</b>
Contacted Researcher	250	-
Recruited into Study (Total)	203	81 (203/250)
Completed Study (Total)	175	86 (175/203)
Completed Paper Study	35	20 (35/175)
Completed Online Study	140	80 (140/175)

A variety of recruitment methods were used. Online advertising was a cheaper and more effective way to reach volunteers compared to newspaper advertising (Table 19). Respondents recruited through “other” methods included responses to the community flyers and word of mouth. Respondents recruited by unknown methods were the least likely to complete the survey.

**Table 19: Cost and Success of Recruitment Methods**

<b>Recruitment Method</b>	<b>n</b>	<b>n completed (%)</b>	<b>Total Cost</b>	<b>Cost Per Recruited Participant</b>
Newspaper	50	43 (86)	\$2,244.06	\$44.88
Online	87	77 (89)	\$255.80	\$2.94
Other	48	43 (90)	-	-
Unknown	18	12 (67)	-	-

### 3.3.2 Demographic Characteristics of Survey Respondents

The demographic characteristics of respondents are presented in Table 20.

**Table 20: Demographic Characteristics of Survey Respondents (total n=175)**

	<b>n</b>	<b>%</b>
<b>Gender</b>		
Female	149	85.1
<b>Age Range</b>		
18-25	42	24.0
26-35	67	38.3
36-49	40	22.9
50-65	24	13.7
Prefer not to answer / blank	2	1.1
<b>Education Level</b>		
Less than high school	5	2.9
High school graduate	10	5.8
Some college or university	30	17.3
College or university graduate (e.g. bachelor's degree)	89	51.5
Post-graduate training (e.g. master's, post-graduate certificates)	39	22.5
No answer	2	1.1
<b>Employment Status</b>		
Employed (full-time or part-time)	97	56.1
Self-employed	15	8.7
Full-time homemaker or student	38	22.0
Unemployed	10	5.8
On disability or social assistance	5	2.9
Other	4	2.3
Prefer not to answer / blank	6	3.4
<b>Ethnic Background</b>		
Caucasian	119	68.2
Asian	24	14.0
African	10	5.8
Other	14	8.1
Prefer not to answer / blank	8	4.6
<b>Nationality and Language</b>		
Born in Canada	119	68.0
English primary language	155	88.6
<b>Gross Household Income</b>		
\$0-30,000	36	20.8
\$30,000-40,000	11	6.4
\$40,000-50,000	17	9.8
\$50,000-60,000	13	7.5
\$60,000-70,000	10	5.8
\$70,000-80,000	5	2.9
Over \$80,000	52	30.1
Prefer not to answer / blank	31	17.7

Greater proportions of respondents were female (85%), spoke English in their home (89%), and were between the ages of 25-49 years (61%). The overall mean age was 34.7 years (SD 11.4). The majority of respondents had a college or university degree, and many (23%) had post-graduate training. The majority of respondents (65%) were employed, and 22% were students or homemakers. Small proportions of respondents were unemployed, receiving benefits, or did not provide an answer. The majority of respondents described themselves as being Caucasian (68%). The second major ethnic group reported was Asian (14%). Further analysis showed that people who were born in Canada were more likely to be Caucasian (85% of those born in Canada were Caucasian, compared to 32% of those born outside of Canada; chi-square statistic  $p < 0.001$ ).

The distribution of gross household incomes of survey respondents was weighted on the extreme ends of the spectrum, with 21% reporting incomes in the lowest bracket of \$0-30,000 and 30% reporting incomes in the highest bracket of over \$80,000. Income levels were related to other demographic variables. People in the highest income bracket were more likely to have completed university (37% of college/university educated or higher had high incomes vs. 11% of less than college/university, chi-square statistic  $p < 0.001$ ). People in the lowest income bracket were more likely to be female (30% of females vs. 12% of males, chi-square statistic  $p = 0.015$ ). A comparison of the demographic characteristics in the sample to the Greater Toronto population is provided in the discussion.

Responses to health-related questions are shown in Table 21. Approximately half (42%) had at least one child; the mean number of children per parent was two (SD 1.3). Nineteen percent of respondents had previously consulted the Motherisk Program and rated their satisfaction with their experience as 3.8 (SD 1.0) on a scale from one (not satisfied) to five (extremely satisfied). Seventeen percent of participants reported currently using anti-depressants. The majority of respondents (94%) reported having their own family doctor.

**Table 21: Responses to Health-related Questions**

	<b>n</b>	<b>%</b>
Have children	73	41.7
Currently pregnant	13	7.4
Called Motherisk before	33	18.9
Have child with birth defect	6	3.4
Have close friend/relative with child with birth defect	64	36.6
On anti-depressants	29	16.6
Have own family doctor	165	94.3
In favour of public funding for TIS	144	82.8

Comparisons were made between the demographic characteristics of various sub-groups. Differences were found between respondents who opted to complete the survey online and those who did it on paper: online respondents were significantly younger, less likely to have low incomes, and more likely to be Asian (Table 22). Sub-group analysis also revealed that the youngest respondents (ages 18-25) were more likely to be students (66% vs. 34% of respondents over 25; chi square statistic  $p < 0.001$ ) and have low incomes (50% vs. 19% of respondents over 25; chi square statistic  $p < 0.001$ ).

**Table 22: Comparison of Online and Paper Respondents**

	<b>Online</b>	<b>Paper</b>	<b>P</b>
<b>n</b>	140	35	-
<b>% Low Income</b>	23	43	0.003*
<b>% Asian</b>	17	0	0.009*
<b>Mean Age (SD)</b>	33.1 (11.0)	41.2 (10.6)	<0.001**

\*Chi-square statistic

\*\*T-test

The majority of respondents reported that they would be anxious about a pregnancy exposed to anti-depressants (89%, see Table 23). When rated on a Likert scale from one (not anxious) to five (extremely anxious), the majority (68%) rated themselves as anxiety level four or five.

**Table 23: Level of Anxiety about Exposed Pregnancy**

<b>Anxiety Level</b>	<b>Description of Level</b>	<b>N</b>	<b>%</b>
Anxiety Level 1	Not anxious	19	10.9
Anxiety Level 2	Somewhat anxious	4	2.3
Anxiety Level 3	Moderately anxious	34	19.4
Anxiety Level 4	Very anxious	74	42.3
Anxiety Level 5	Extremely anxious	43	24.6
Missing		1	0.6

Anxiety levels were related to some demographic characteristics. People who rated themselves as extremely anxious (score of five) were more likely to have children than all other anxiety levels (60% of extremely anxious people had children compared to 36% for the rest of the sample; chi-square  $p=0.005$ ). Anxiety was measured on a Likert scale and not a validated measure of anxiety.

### 3.3.3 Regression Models

The results of the main effects logit regression model are presented in Table 24 (modeling the attributes only). In the SAS analysis, predictor variables were dummy coded. In dummy coding, the reference level is coded as zero and the other level is coded as one.

As expected, respondents preferred to receive information that is very helpful, have confidence in the skills of the IP, and to meet with an IP that knew them and their medical history. Interestingly, respondents preferred to speak with an IP who was a counselor with specialized training in medication use during pregnancy rather than a family doctor with general training and to call a telephone service rather than have an in-person appointment. The directions of preferences were the same as in the pilot study, except for the training of the IP. All attributes were significant at the 5% level, except for the difference between the \$10 and \$50 level in the cost attribute, indicating that respondents did not have significant negative utility for the \$50 level. The beta coefficients for the cost attribute did not show a linear relationship. .

**Table 24: Results of Main Effects Multinomial Logit Regression Model**

Attributes	Levels	Beta Estimate*	SE	95% CI		Pr >Chi sq
				Lower	Upper	
Type of training of Information Provider (IP)	Counselor with specialized training	0.134	0.053	0.030	0.238	0.012
	Family doctor	-				
Counseling method & waiting time	Call telephone service	0.109	0.054	0.004	0.215	0.043
	Make appointment	-				
Knowing the IP	Have met the IP before & they know your medical history	0.418	0.055	0.311	0.525	<.001
	The IP is not known to you	-				
Confidence in the skills of the IP	Have confidence in the skills of the IP	0.519	0.054	0.413	0.624	<.001
	Unaware of the skills of the IP	-				
Helpfulness of information	Enough information has been provided	1.147	0.056	1.037	1.258	<.001
	Some information has been provided	-				
Cost to you	\$10	-				
	\$50	-0.041	0.075	-0.188	0.106	0.587
	\$90	-0.536	0.073	-0.680	-0.392	<.001

SE=Standard error; CI=Confidence interval

\* (-) denotes the reference level

### 3.3.3.1 Interaction Model

Significant interactions were identified between preferences for attributes and respondent demographic characteristics. Initially, 36 interaction variables were identified when terms were added one at a time. When all 36 variables were run with the base model, several were dropped as they became statistically insignificant. Nine interaction terms were eventually found to be significant. Some of these interaction terms were three-level categorical variables. To facilitate interpretation, these three-level variables were re-coded into two-level variables (for example, high income, low income, and income not reported were re-coded to low income and not low income). This resulted in a loss of degrees of freedom, but the two models were not significantly different (see Table 25 and Table 28). In the interaction model, the difference between the \$10 and \$50 became significant, indicating that linearity was improved under this model.

**Table 25: Regression Model Including Significant Interactions with Demographic Variables**

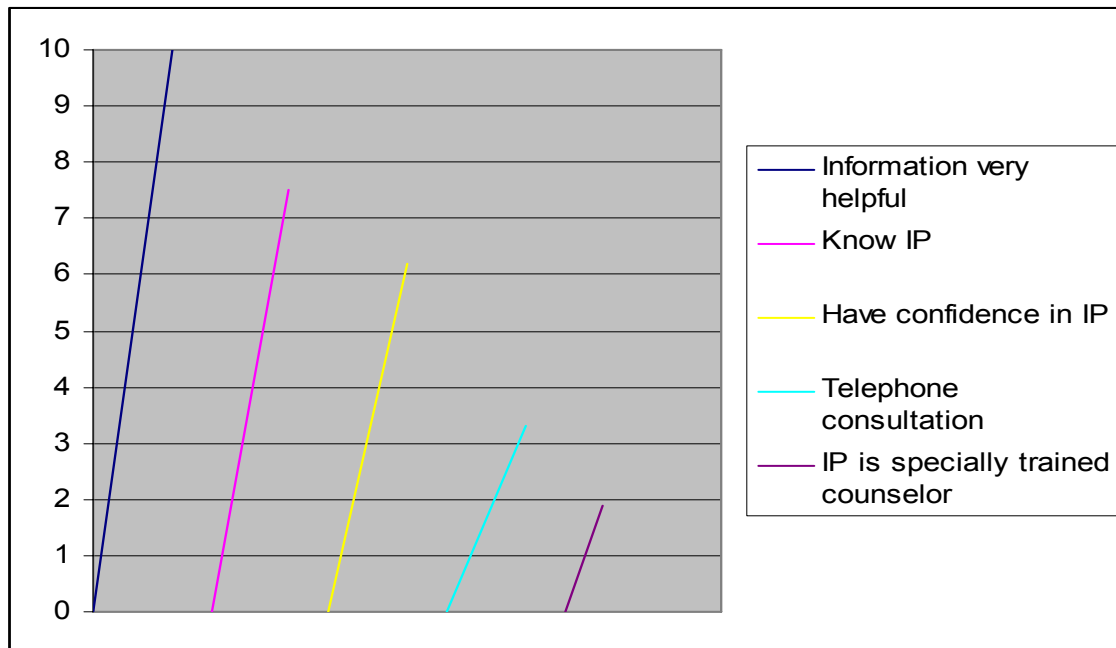
Attribute	Beta Estim.	SE	95% CI		Pr > Chi Sq	Interpretation
			Lower	Upper		
Training (Counselor)	0.133	0.067	0.001	0.264	0.049	Counselor preferred over family doctor
Method (Telephone)	0.231	0.080	0.074	0.388	0.004	Telephone preferred over in-person visit
Knowing (IP is known)	0.528	0.063	0.405	0.651	<.001	Knowing the IP preferred over not knowing them
Confidence (confident in IP)	0.433	0.102	0.234	0.632	<.001	Having confidence in the IP preferred over being unaware
Helpfulness (Info. is very helpful)	0.717	0.101	0.518	0.915	<.001	Receiving very helpful info. preferred over somewhat helpful info.
Cost 0 (\$50)	-0.273	0.135	-0.537	-0.009	0.043	Paying \$50 is worse than \$10
Cost 1 (\$90)	-0.977	0.136	-1.243	-0.710	<.001	Paying \$90 is worse than \$50
Helpfulness * Education	0.763	0.117	0.533	0.992	<.001	People with more education had greater preference for very helpful info.
Cost 0 * Anxious	0.341	0.163	0.023	0.660	0.036	People with high levels of anxiety about the exposure were willing to pay more
Cost 1 * Anxious	0.616	0.162	0.299	0.934	<0.001	
Knowing * Motherisk Caller	-0.434	0.137	-0.702	-0.166	0.002	Previous Motherisk callers had lesser preference for knowing the IP
Helpfulness * Other Race	-0.346	0.137	-0.615	-0.078	0.012	People of ethnicities other than Caucasian/Asian had a lesser preference for very helpful info.
Training* Motherisk Caller	0.369	0.137	0.101	0.638	0.007	Previous Motherisk users had greater preference for an IP counselor
Confidence * Unemployed	-0.385	0.153	-0.685	-0.084	0.012	Unemployed people had lesser preference for confidence in IP
Training * Other Race	-0.342	0.137	-0.611	-0.072	0.013	People of ethnicities other than Caucasian/Asian preferred an IP who is a family doctor
Method * Low Income	-0.218	0.109	-0.430	-0.005	0.045	People with low incomes preferred an appointment rather a telephone consultation
Confidence * Anxious	0.237	0.117	0.008	0.467	0.043	People with high levels of anxiety had greater preference for confidence in the IP

SE=Standard error; CI=Confidence interval; estim.=estimate

The interactions are shown in Table 25 in descending order of Wald Chi-square value (not shown). Of particular interest was the finding that education affected the strength of preference for very helpful information. Motherisk users more strongly preferred having a specially trained counselor, and had no preference for knowing the IP, compared to the overall sample. People of race other than Caucasian or Asian had a preference for the training of the IP that was opposite to the rest of the sample: they preferred to speak to a family doctor.

As utility has no natural scale, the utilities derived from the interaction model for the five service attributes were scaled onto a zero to ten scale to facilitate interpretation. The largest gain in utility was obtained when information was very helpful; the amount of utility gained by obtaining the preferred level for this attribute was set to ten, and all other utility values were scaled upwards by the same amount to demonstrate how much utility is gained for the other preferred levels compared to the information attribute (for example, the utility for receiving very helpful information was 0.7071; to scale this number to ten it needs to be multiplied for 14.14). All utilities were then multiplied by 14.14). The relative utility gains for obtaining each preferred level are presented in Figure 4.

**Figure 4: Relative Utility Gains for Preferred Levels**



### 3.3.3.2 Two-Way Interactions between Attributes

Some two-way interactions were expected, particularly for some of the more subjective and related attributes such as knowing the IP and having confidence in the IP. If two-way interaction terms were found to be significant and subsequently added to the regression model, the other beta estimates would be affected; it is difficult to estimate to what extent and in what directions beta estimates are affected by including significant interaction terms if they exist.

Sawtooth was used to explore potential two-way interactions. Five potential interactions were identified using count analysis (a simple analysis method that calculates a proportion of "wins" for each level, based on how many times a concept including that level is chosen, divided by the number of times a concept including that level appeared in the choice task) [280]. When these interactions were added one at a time to the logit model, the difference in log likelihood did not indicate a significant improvement to the model. The largest improvement was seen with the interaction between helpfulness and cost (p value approximately 0.2). A different design strategy may have allowed for estimation of two way interactions. As previously mentioned this is a potential limitation of the design. If two way interactions had been included and were found to be significant, they can improve the fit of the model [268]. A commonly used example of an interaction may be an increased preference for a sports car brand if the colour of the car is red. Such an interaction will affect the individual utilities for brand and colour. It is difficult to estimate what impact interactions might have had on the utilities estimated in the current study.

### 3.3.3.3 Willingness-to-Pay

Willingness-to-pay was calculated by dividing the beta estimates by the marginal utility of money. The marginal utility of money was calculated by taking the slope through the three data points representing the cost and utility of the levels used in the study, presented in Table 26. The calculation of WTP is based on the assumption that utility is linear, meaning that each additional unit change has the same marginal effect on choice [278]. This assumption is common to choice models [214], but as will be seen may not always be accurate.

**Table 26: Calculation of the Marginal Utility of Money**

X-axis coordinates	Y-axis coordinates	Slope through all 3 points	Slope through last 2 points (SA)
\$10	0	-0.012	
\$50	-0.273		-0.018
\$90	-0.977		

SA=Sensitivity Analysis

Based on this calculation, the slope representing the marginal utility of money was -0.012. It was observed that the line was not straight, and that the utility decrease moving from \$50 to \$90 was steeper than moving from \$10 to \$50 even though the increment in cost was the same, implying that each additional unit change had a different marginal effect on choice. The slope was calculated for the two data points representing \$50 and \$90 in a sensitivity analysis. WTP estimates are shown in Table 27.

**Table 27: Willingness-to-Pay Based on Interaction Model**

Attribute	Beta Estimate	WTP (\$)	95% CI		SA WTP (\$)
			Lower	Upper	
Training (Counselor)	0.133	11	6	16	8
Method (Telephone)	0.231	19	13	26	13
Knowing (IP is known)	0.528	43	36	54	30
Confidence (Have confidence in IP)	0.433	35	26	45	25
Helpfulness (Info. is very helpful)	0.717	59	48	74	41

SA=Sensitivity Analysis

Dividing the beta parameters for the attributes in the interaction model by the marginal utility of money found that WTP to speak with a specially trained counselor was \$11, to receive the information rapidly by telephone was \$19, to have confidence in the IP was \$35, to speak with a known IP was \$43, and to receive information that is very helpful was \$59. Receiving very helpful information was about twice as valuable as having confidence in the IP, three times as valuable as choosing the appointment method, and six times more valuable than choosing the training of the IP. Speaking with a known IP was about twice as valuable as appointment method and four times as valuable as choosing the training of the IP.

### 3.3.3.4 Sensitivity Analysis of Marginal Utility of Money and Confidence Intervals

As previously described, a sensitivity analysis was conducted where a slope was calculated using only the values for the \$50 and \$90 levels. This resulted in WTP amounts being reduced by approximately 30% (see Table 27). In the bootstrapped datasets, linearity for the cost variable was improved due to the larger sample size (sample sizes of 1000 were bootstrapped from the original 175). Therefore, some of the sensitivity analysis WTP values are lower than some of the lower 95% CIs from the primary analysis.

### 3.3.3.5 Model Fit Statistics

Model fit statistics were examined for the base model and the interaction model (two interaction models were run, one with three-level categorical variables and one with two-level categorical variables). McFadden's Pseudo  $R^2$  was between 0.2-0.4 for all models, indicating an acceptable goodness of fit (see Table 28) [291]. Adding the interaction terms resulted in a significant improvement in the model, shown by the decrease in Log Likelihood. The joint significance of the interaction terms not included in the model was greater than 0.05 (not significant). Re-coding categorical variables from three to two levels did not significantly change the model. The likelihood ratio chi-square for all models was  $p < 0.001$ .

**Table 28: Model Fit Statistics**

Model #	Description of Model	-2 LogL Without Co-variables*	-2 LogL With Co-variables*	Mc-Fadden's Pseudo R <sup>2</sup>	Difference in LogL of Full & Reduced Models	DF	P**
1	Main effects model	2888	2187	0.243	-	7	-
2	Model with interactions as 3-level variables	2888	2079	0.280	108.1 (#2 compared to #1)	21	<0.001
3	Model with interactions as 2-level variables	2888	2083	0.279	4.2 (#3 compared to #2)	17	NS
4	Model with all non-significant interactions	2888	2155	0.254	32.2 (#4 compared to #1)	55	NS

DF=Degrees of Freedom

NS= p greater than 0.05

\*Rounded to zero decimal places.

\*\*Based on the difference between the full and reduced models being a chi-square statistic with DF equal to the difference in DF between the two models (see DF column).

### 3.3.3.6 Stratified Regression Analyses

Stratified regression models were created to further assess the impact of demographic variables on preferences. The sample was split according to the variables of education and anxiety. Individual base models (i.e. including only the six attributes in the regression analysis) were created for these groups.

#### 3.3.3.6.1 Interaction between Level of Education and Helpfulness of Information

The beta estimates and WTP for the preferred attribute levels are shown in Table 29 (WTP calculated by the same method as described in Section 3.2.5.9). People with more education were willing to pay about twice as much as people with less education to know the IP, have confidence in the IP, and receive very helpful information. People with less education were willing to pay twice as much as those with high educations to speak with an IP who is a specially

trained counselor. These models are based on small sample sizes so should be interpreted with caution, but are useful for demonstrating differences in WTP between different groups.

**Table 29: Regression Model Stratified by Education**

	<b>Main Effects Model (n=175)</b>	<b>WTP (\$)</b>	<b>High Education (n=128)*</b>	<b>WTP (\$)</b>	<b>Low Education (n=47)*</b>	<b>WTP (\$)</b>
Training (Couns.)	0.134	20	0.093	15	0.245	29
Method (Tele.)	0.109	16	0.115	18	0.106	13
Knowing (known)	0.418	62	0.481	76	0.330	41
Confidence (Have)	0.519	77	0.593	94	0.402	49
Helpfulness (Very)	1.147	171	1.382	219	0.637	77
Cost \$50	-0.041		-0.102		0.046	
Cost \$90	-0.536		-0.505		-0.651	
Total WTP		347		422		210

WTP=Willingness-to-Pay

\*Main Effects Model

### 3.3.3.6.2 Interaction between Anxiety Level and Cost

Respondents were segmented into four categories: not anxious (level zero), anxiety level three (moderately anxious), anxiety level four (very anxious), and anxiety level five (extremely anxious). As anxiety decreased, the beta estimates for the cost levels decreased; simply, the less anxiety people felt, the less they were willing to pay (see Table 30). Once again, caution is to be exercised in interpreting these stratified results as the sample sizes are quite small. There is a clear relationship, however, between anxiety and WTP.

**Table 30: Change in Cost Coefficient by Respondent Level of Anxiety about the Pregnancy Exposure**

	<b>Not anxious (n=19)*</b>	<b>WTP (\$)</b>	<b>Moderately anxious (n=34)*</b>	<b>WTP (\$)</b>	<b>Very anxious (n=74)*</b>	<b>WTP (\$)</b>	<b>Extremely anxious (n=43)*</b>	<b>WTP (\$)</b>
Training (Couns.)	-0.085	-5	0.070	7	0.182	38	0.219	68
Method (Tele.)	0.195	13	0.064	6	0.169	35	0.027	8
Knowing (known)	0.193	12	0.498	48	0.472	97	0.406	126
Confidence (Have)	0.462	30	0.329	32	0.590	122	0.654	202
Helpfulness (Very)	0.850	55	1.221	119	1.199	248	1.120	347
Cost \$50	-0.633		-0.101		0.003		0.175	
Cost \$90	-1.240		-0.825		-0.387		-0.258	
<b>TOTAL</b>		105		212		539		751

WTP=Willingness-to-Pay

\*Main Effects Model

### 3.3.4 Dominant and Illogical Decision Makers

Responses to choice tasks were examined to determine if any respondents exhibited dominance.

Full dominance was considered to occur if the respondent always chose based on one level.

Partial dominance was considered to occur if the respondent chose based on one level in 11/12 choice tasks. These results are shown in Table 31.

**Table 31: Dominant Decision Makers**

<b>Level</b>	<b>Number of Respondents (%)</b>	
	<b>Full</b>	<b>Partial</b>
Family Doctor Dominant (always chose doctor)	2 (1.1)	2 (1.1)
Telephone Consultation Dominant (always chose telephone)	1 (0.6)	3 (1.7)
Cost \$90 Dominated (never chose \$90)	12 (6.9)	11 (6.3)

Overall, few people failed to choose the objectively better scenario, however respondents were worse at the second best/worst task, potentially indicating fatigue (Table 32). Only two respondents picked the worst scenario in both tasks.

**Table 32: Illogical Decision Makers**

	<b>Number of Respondents (%)</b>
Picked worst case scenario in first task	4 (2.3)
Picked worst case scenario in second task	8 (4.6)
Picked worst case scenario in both tasks	2 (1.1)
Picked worst case scenario in at least one task	8 (4.6)

Once the dominant and illogical decision makers were identified, the main effects regression model (i.e. attributes only, not including demographic interactions) was run again with these people excluded (see Table 33). Excluding the illogical and dominant respondents did not significantly affect the beta coefficients except for cost. As would be expected, when the cost dominators were excluded, the utility of cost increased (i.e. less aversion to high cost). Similarly, there was an increase in preference for speaking with a specially trained counselor when the family doctor dominators were removed. There are no clear guidelines on how to handle these respondents, as their preferences may be valid and just different from our general expectations, with unique decision-making heuristics [296]. McFadden's pseudo  $R^2$  was not altered by deleting illogical or dominant responders. Therefore, the dominant and illogical respondents were retained in the overall analysis.

**Table 33: Impact on Regression Model of Excluding Dominant and Illogical Decision****Makers**

	<b>Main Effects Model</b>	<b>Removed those who failed both best/worst tasks (n=2)</b>	<b>Removed those who failed at least one best/worst task (n=10)</b>	<b>Removed those who were cost dominant (n=23)</b>	<b>Removed those who were telephone dominant (n=4)</b>	<b>Removed those who were family Dr. dominant (n=4)</b>
Training (Couns.)	0.134	0.130	0.111	0.125	0.138	0.197
Method (Tele.)	0.109	0.112	0.107	0.123	0.055	0.105
Knowing (known)	0.418	0.433	0.459	0.509	0.423	0.410
Confidence (Have)	0.519	0.535	0.556	0.571	0.535	0.507
Helpfulness (Very)	1.147	1.176	1.250	1.239	1.177	1.182
Cost \$50	-0.041	-0.060	-0.107	0.019	-0.039	-0.059
Cost \$90	-0.536	-0.556	-0.612	-0.266	-0.542	-0.580
-2LogL with covariates	2186.7	2137.1	1978.8	1860.9	2108.9	2112.7
-2LogL without covariates	2887.7	2855.8	2722.7	2523.1	2821.1	2821.1
McFadden's Pseudo R <sup>2</sup>	0.243	0.252	0.273	0.262	0.252	0.251

While it is possible that the illogical decision makers have their own unique decision-making heuristics, they were more likely to have a lower education level (see Table 34). Their ethnicity distribution was also different from the overall sample.

**Table 34: Demographic Characteristics of Illogical Decision Makers**

	<b>Illogical Decision Makers (n=10)</b>	<b>Logical Decision Makers (n=164, 1 missing)</b>	<b>P*</b>
% Low Education**	50%	25%	0.082
% Caucasian	50%	70%	0.014
% Asian	0%	15%	
% Other Race	50%	15%	

\*Chi square test.

\*\*Less than college/university education.

The demographic characteristics of cost dominators were also different from the overall sample. Cost dominators were more likely to have a low education level, to have previously consulted the Motherisk program, and to select cost as the attribute they would choose if they could base their decision on one attribute (Table 35). These relationships held when the cost dominators who never chose a scenario with \$90 were examined (total cost dominators) and when the respondents who only once chose a scenario with \$90 were included (partial cost dominators).

**Table 35: Demographic Characteristics of Cost Dominators**

	<b>Total Cost Dominant (n=12)</b>	<b>Non Dominant (n=163)</b>	<b>P*</b>	<b>Partial Cost Dominant (n=23)</b>	<b>Non Dominant (n=152)</b>	<b>P*</b>
% Low Education <sup>+</sup>	58%	25%	0.011	52%	23%	0.003
% Previous Motherisk Caller	42%	17%	0.038	36%	16%	0.026
% Cost Most Impt. Attribute	17%	2%	0.039**	13%	1%	0.017**

\*Chi-square test.

\*\*Fisher's exact test.

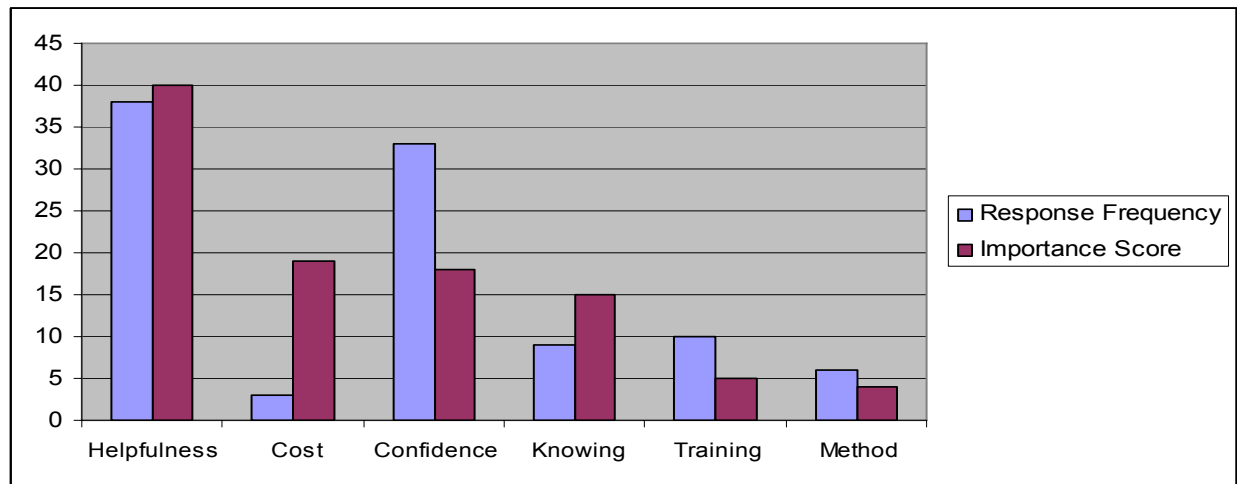
<sup>+</sup> Less than college/university education.

### 3.3.5 Importance Scores versus Choice of Most Important Attribute

In the demographic section of the survey following the choice tasks, respondents were asked upon which attribute they would base their decision if they could only choose one (essentially, what is the most important attribute in making the choice of service). Response frequencies showed a very similar distribution to the distribution of the beta estimates in the main effects model, with some important differences (Table 36). Helpfulness of information was most often chosen as the most important attribute, followed by confidence in the skills of the IP. Cost was least often chosen as most important, however it had the second highest importance score in the regression model. There was reasonable correlation between the response frequencies and importance scores ( $r=0.730$ ). When the cost attribute was left out, the correlation improved to  $r=0.855$ . In the way the follow-up question was worded, there was no cost level attached to the attribute description, just "cost", which may have had an effect on its perceived importance. The relationship between the two importance ratings is presented graphically in Figure 5.

**Table 36: Choice of Most Important Attribute Compared to Importance Scores**

Attribute	Beta	Importance Score	Response Frequency % (n)
Helpfulness of Info.	1.147	40	38 (66)
Cost	0.536	19	3 (5)
Confidence in IP	0.519	18	33 (57)
Knowing IP	0.418	15	9 (16)
Training	0.134	5	10 (18)
Method	0.109	4	6 (11)
<b>Total</b>	<b>2.863</b>	<b>100</b>	<b>173 (2 missing)</b>

**Figure 5: Comparison of Importance Score with Response to Explicit Choice of Most Important Attribute**

### 3.3.6 Comparison of Fixed Choice Task Responses to Utility for Specific Scenarios

A fixed choice task with levels best representing a counseling experience at a TIS and a counseling experience at a family doctor's office was included. Approximately 55% of the time the TIS was chosen. The utility of the two scenarios were compared (Table 37).

**Table 37: Responses to Fixed Choice Task Comparing TIS and Family Doctor**

<b>Attribute</b>	<b>TIS</b>	<b>Family Doctor</b>
Training	Counselor	Family Doctor
Method	Telephone	Appointment
Know	Stranger	Know
Confidence	Know nothing	Have confidence
Helpfulness	Very helpful	Somewhat helpful
Cost	\$50	\$10
Utility (sum of main effects model coefficients)	1.349	0.937
Survey Responses to Fixed Choice Task	54.6	45.4

Interestingly, the utility for the TIS scenario described in the fixed choice task is slightly higher than that for the family doctor scenario, which is the same as what was observed in the responses to the fixed choice tasks. Similarly, in Table 38 it is shown that the utility for the best case scenario is much greater than the worst case scenario, and it was rarely chosen in the fixed choice task.

**Table 38: Comparison of Best and Worst Service Scenarios**

<b>Attribute</b>	<b>Worst Case</b>	<b>Best Case</b>
Training	Family Doctor	Family Doctor
Method	Appointment	Appointment
Know	Stranger	Know
Confidence	Know nothing	Have confidence
Helpfulness	Somewhat helpful	Very helpful
Cost	\$90	\$10
Utility (sum of main effects model coefficients)	-0.536	2.084
Survey Responses to Best-Worst Fixed Choice Task	3.4	96.6

### 3.3.7 Real Life Use of Information Sources

Respondents were asked to check all information sources they might consult if they had this question in real life. Responses to this question are shown in Table 39.

**Table 39: Responses to Question: “Check all information sources you would consult”**

<b>Information Source</b>	<b>Number of Respondents That Chose Source (%)</b>
Family Doctor	162 (93.1)
TIS	157 (90.2)
Internet	146 (83.3)
Obstetrician	140 (80.5)
Books	130 (74.7)
Family & Friends	110 (63.2)
Telehealth	78 (44.8)
Genetic Counselor	49 (28.2)
Walk-in Clinic	36 (20.7)

Not only were both family doctor and TIS very frequently picked, 148 people (85%) picked both those sources. Chi-square tests revealed some significant effects of demographic characteristics on choice of information sources. People with high incomes were more likely to select internet and obstetrician. People born in Canada were also more likely to select obstetrician. People with extreme anxiety levels were less likely to select family and friends. Telehealth was more likely to be chosen by people of child-bearing age (26-49) and less likely to be chosen by the youngest age group (18-25). A walk-in clinic was less likely to be chosen by people who were employed. The total number of sources chosen was also examined (Table 40). The majority of people chose multiple sources. People who picked few sources had some specific demographic characteristics: they were more likely to be unemployed, to not report an income, and be on anti-depressants.

**Table 40: Distribution of Number of Sources Picked**

<b>Number of Sources Picked</b>	<b>n (%)</b>
Picked Few Sources (0-3)	18 (10.3)
Picked Some Sources (4-6)	97 (55.4)
Picked Many Sources (7-9)	60 (34.3)

### 3.4 Discussion

The majority of survey respondents were women of a higher socio-economic status who opted to use the online platform. The results showed that the helpfulness of information was the most important attribute influencing choice of information service; the methods by which information was delivered were far less important. A detailed discussion of the main results follows.

### 3.4.1 Comparison of Demographic Characteristics of Sample with Greater Toronto Population

A comparison of the education levels of the sample to the results of the 2006 Canadian census results for the Greater Toronto Area (GTA) showed that the sample was more highly educated than the GTA population. Only 9% of survey respondents had a high school diploma or less, compared to 45% of the GTA population aged 15 and over [297]. The survey sample was also less ethnically diverse than the GTA. There was a higher proportion of Caucasians in the sample. Additionally, the majority of survey respondents reported being born in Canada with only about half of Toronto residents reported as non-immigrants in the 2006 census [297]. The majority of survey respondents (89%) reported speaking English primarily in their home, which is also a higher proportion than found in the GTA [297]. The median income in GTA households in 2005 was \$52,833 [297] and \$50-60,000 was the median income range in this sample amongst those who reported an income. The low-income cut off used by Statistics Canada as measure of poverty for people living in a 4-person household in 2002 dollars was \$36, 235 [297]. It appeared that many of the people in the survey who reported low incomes were also university students. Students may be living on low incomes during their studies, however there are likely many differences between them and a person who lives in poverty, therefore it should be assumed that the sample did not represent preferences of people with low incomes. It was found that 17% of the survey respondents were currently using anti-depressants. Estimates of anti-depressant use vary widely so it is unknown whether this is within the normal range. The national rate of antidepressant use in Canada has been estimated at 6% [298]. It has also been estimated that 13% of all pregnancies in America will be exposed to anti-depressants [262].

### 3.4.2 Preferences for Teratology Counseling

The magnitude and directions of preferences for attributes of teratology counseling following an exposure to anti-depressant medication during pregnancy were estimated in this DCE. Not surprisingly, the most important attribute of the counseling was the provision of information that is very helpful. The most interesting aspects of the results were the direction and size of preferences and the interactions with demographic variables.

It was previously unknown whether people would prefer to speak with an IP that knows them or if they would prefer to remain anonymous. This survey found that people would prefer to speak

with someone with whom they have familiarity, and that this feature was almost as important as receiving very helpful information. Similar results were found in a DCE of primary care, which found that the most important attribute was to receive a thorough examination, followed by seeing a physician that knew the patient well [299]. Several DCEs evaluating family practice medicine have found that respondents would wait longer to see a familiar medical practitioner who was well informed about their case, particularly when it was a new or uncertain condition [240, 300, 301]. Although focus group participants stated they might prefer anonymity as it reduces embarrassment around discussing sensitive issues, overall this study found that familiarity was an important feature of counseling. It was, however, valued less by people that had previously used the Motherisk service, so it is possible that preferences change depending on prior experiences with anonymous services.

The finding that people preferred to speak with a specially trained counselor rather than a family doctor was in the opposite direction of previous studies which have generally found that a GP is preferred [236, 238, 301, 302]. An evaluation of out of hours GP care found that respondents were willing to wait an extra hour to see a doctor rather than a specially trained nurse [237]. A study of practice nurse vs. doctor-led primary health care for minor illness found that women, younger people, the less well-educated and those with higher incomes had a more positive attitude towards the nurse, whereas older people had a more positive attitude to the doctor [238]. Doctor shortages are common in Canada and in other western nations with publicly administered health care systems, and recent years have seen a shift towards increased roles of nurses and pharmacists in the delivery of primary care [303]. Preferences for training of the IP may evolve as people become more familiar with different primary care models. Similarly, our study found that subgroup preferences for training of the IP varied.

Training of the IP was not rated as a highly important attribute by the focus groups, and subsequently was found to be the smallest factor influencing choice (WTP \$11). However, it was an important attribute to include as it is one of the main differences between counseling by TIS and physicians. Method of consultation was also not rated highly by focus groups nor was it found to be very important in the regression analysis (WTP \$19), but it is also an important difference between services. Relative to the other attributes, both the training of the information provider and the method of consultation were less important features of the counseling.

### 3.4.3 Influence of Demographic Factors on Preferences

Interesting interactions between preferences and demographic characteristics were found. Subgroups were identified (dominant decision makers and people of non-Caucasian or Asian ethnicity) for whom a family doctor was the preferred IP, which was a preference in the opposite direction of the overall sample. TIS and other alternative services should be aware that such subgroups may exist. The doctor-patient relationship can be very powerful [296, 304]. People may achieve greater reassurance in speaking with a physician depending on their attitudes towards physicians and their personal experiences.

It was found that people with higher levels of education had greater utility for obtaining information that is very helpful compared to people of lower levels of education. It is well known that a social gradient in health exists [305]. Several reasons have been postulated for this, including Grossman's model of the demand for health capital. Grossman's model assumes that people with more education are more efficient producers of health [158], perhaps because they are able to extract more value from the health information they receive and are better able to navigate the health care system. This study found that not only may people of a higher education level extract better value from health information, but that they may have a higher demand for health information in the first place. This is an important finding, as health agencies and providers may need to come up with ways to better engage people with lower levels of education when communicating health information. It is generally believed that TIS users are of a higher socio-economic status than the general population [157, 306, 307].

The underlying reasons for reduced demand among less educated people are likely complex. Perhaps, as postulated by Grossman [158], people with less education extract less value from health information. It is possible that people with lower levels of education become more reliant on their HCPs, rather than seeking information themselves. In the stratified regression analysis, less educated people had lower utility for almost all attributes except for training of IP. Caution must be exercised in interpreting the significance of the stratified regression analyses as segmenting the sample reduced the sample size available for analysis.

The interaction between anxiety level and cost is logical and in an expected direction, potentially demonstrating that people were considering their answers carefully. This range may be useful for estimating WTP for different types of inquiries. Interestingly, income did not interact with the

cost attribute, probably because this was a one-time expenditure that was not very expensive. Previous studies have found interactions between income and WTP, but for more costly interventions [169, 214]. One of the main reasons that WTP and CBA fell out of favour in the health economics field is that since WTP is tied to ability to pay, interventions benefiting people of less ability to pay may be undervalued, leading to inequity [308]. This study found that WTP may not always be related to ability to pay, especially for one time expenditures that are relatively small, but WTP can be related to other factors.

There was an interesting interaction between unemployment and preference for method of contact, which suggests that when people have more flexible schedules they may be more partial to in-person appointments. During survey development, merging the waiting time and method attributes into one attribute was a decision made to simplify the questionnaire, however it becomes difficult to draw conclusions as to whether people in reality prefer face to face appointments or were mainly motivated by the shorter waiting time of a telephone consultation. A previous study found a similar interaction in that employed people had a stronger preference for choice of appointment time with their GP, and were willing to wait longer when they could choose the appointment time [300]. An evaluation of satisfaction with telemedicine primary care found that satisfaction with the experience was very high (>90%), and participants did not report that the telemedicine format interfered with their relationship with the health care provider [309].

The large number of interactions with demographic variables suggests that subgroups exist with distinct preferences. In future, a latent class analysis of these data may be useful in further defining population preferences for teratology counseling. In a latent class analysis, respondents are divided into segments that have similar preferences; this type of analysis is more commonly used in marketing research than in health care, but may be suitable in areas such as this where preferences are more subjective. Indeed, a latent class analysis of children's mental health professionals found three distinct groups whose preferences differed with respect to how they believed information about child mental health services should be delivered to parents [310]. A review of preferences for primary health care found that patient characteristics often interact with preferences, particularly age and economic status, and less frequently education, health status, family situation, sex, and utilization of health care [311].

The exposure being evaluated was for an anti-depressant. As previously mentioned, people may have different attitudes towards psychological medications compared to others [159]. It was found that most survey respondents felt anxiety about this exposure. This may limit the generalizability to preferences and WTP for other types of exposure, where the medication is question is less stigmatized and may provoke less anxiety. It was also found that WTP was related to level of anxiety, with increased anxiety resulting in increased WTP. It is likely that a portion of the benefit users obtain from a teratology counseling encounter is related to a reduction in anxiety. If anxiety were to be measured on a Likert scale, it is unclear whether WTP is related to a relative drop in anxiety levels or if anxiety has to be above a certain threshold before reducing it is valued. It could be assumed, however, that preferences and WTP for counseling about exposures that provoke similar anxiety levels to anti-depressants would be similar to those found in this study.

In consideration of the findings of this DCE, TIS should emphasize the high quality of information that they are able to provide as this was the most important attribute. It was found that people preferred speaking with an IP that they know. As the IP at TIS is always going to be unknown to the caller due to the telephone hotline format, this is a potential factor that may limit people's preference for using TIS. Overall, preferences were in favour of features of TIS (such as method of contact and training of the IP). TIS may also want to consider ways in which they can instill confidence in their skills amongst potential users, as this attribute was the third most valued in the interaction model. In the survey of North American TIS it was found that TIS with productive research programs received more calls, which could potentially be related to having a higher profile in their communities, instilling greater confidence in their service and facilitating expectations of the service having high quality information. Prior experience with TIS altered preferences, as Motherisk callers obtained less utility from knowing the IP and more utility from speaking with a specially trained counselor.

#### 3.4.4 Validity of Discrete Choice Experiments

Asking respondents what they felt was the most important attribute provided an interesting opportunity to examine the overlap and disparities between the order of preferences in the regression model and people's explicit choices. While the regression revealed cost to be a very important attribute, it was least often explicitly chosen as important by the respondent. People

may have felt self-conscious about identifying cost for fear of appearing “cheap”. Conjoint analysis can be extremely useful for estimating embarrassing or socially unacceptable biases. One research group found that people would rather have a potential trivia game teammate who was thin rather than overweight, and in fact were willing to trade 11 IQ points to have a thin teammate [312]. The same group has unpublished data showing that undergraduate students would rather have a future boss who was male rather than female [312]. This is an example of why DCEs are a useful method in establishing preferences, as underlying biases may be more easily quantifiable. This method may help avoid the limitations of other survey formats where respondents attempt to answer in a way that they believe is more pleasing or acceptable.

The close correspondence between actual choices to the fixed tasks and the estimated utility of those scenarios suggests that the model is valid. It was interesting to note, however, that even though TIS features were preferred in the regression model, the family doctor was still the most often chosen source of “real life” information (but just barely, 93% of respondents chose it as an information source, whereas 90% chose TIS). Responses to the real life sources of information question confirmed that family doctor is the most logical comparator service to TIS. The high frequency of selection for the top five information sources indicates that there is diverse information seeking behaviour in this context. This finding supports the decision to not offer a none option. However, this may be a limitation of the design because the respondent was forced to choose only one of two services whereas in real life they may consult multiple sources. It was interesting to note that people using anti-depressants were more likely to choose few information sources. Perhaps this was because they already have a relationship with the medication prescriber so they do not feel the need to seek as many information sources. Or, if they are still depressed, they may have decreased motivation to seek out information.

The validity of DCEs is being actively considered in the scientific literature as the method gains popularity. Test-re-test reliability has been found to be high; respondents given a discrete choice survey three times with many questions repeated generally answered in an identical fashion on each questionnaire [168]. Another empirical investigation of internal validity of discrete choice responses found that only 6% of respondents were what the authors deemed “intransitive”; i.e., that if the respondent had previously picked choice A over B and had picked choice B over C, then they should pick choice A over C later in the questionnaire [313]. Such a low level of intransitivity suggests that the preferences being elicited are indeed rational.

### 3.4.5 Limitations and Methodological Issues

There are some limitations to the WTP estimate. It has been suggested that WTP estimates generated by conjoint analysis studies are sensitive to the modeling framework, and to the number and ranges of levels used [314-316]. Calculating the marginal utility of money assumes a linear relationship between cost and utility, however this may have not been the case. In the main effects model, there was little disutility associated with the \$50 level, indicating that respondents did not see this level as being very different from \$10. Perhaps this was seen as an affordable one-time expenditure. While some respondents dominated at the \$90 level, including one level above \$90 could have improved the WTP estimate. Previous DCEs that have varied levels of attributes have found that while other parameter estimates remain stable when levels are varied, WTP is very sensitive to the levels used [317]. In retrospect, the ceiling cost mentioned by the focus groups was \$100, so a value over that could have been included in order to test the limits of WTP. Research has suggested that respondents may be more sensitive to price when it is presented as the last attribute [265]. This is one of many methodological issues regarding the appropriate use of DCEs to assess WTP that must still be addressed in future research [318]. One of the main limitations of stated preference methods is that they are evaluations of hypothetical situations. If the hypothetical situation is incorrectly specified, particularly with respect to cost, the estimates of benefit will also be incorrect.

As described in the methods section, a “none” option was not provided, which could have led to over-estimation of preferences and WTP. As previously mentioned, the selection of real life information sources showed that most people were likely to consult multiple sources of information, therefore having them choose a “none” option likely wouldn’t reflect real life activities. Perhaps three service options could have been presented, with one being a fixed option with levels always representing a family doctor’s visit and the other two scenarios being varied (the family doctor scenario could potentially be labeled as such). A survey in this format would need extensive pilot testing, but may go some way to addressing the need for some people to “opt out” of extra services while also defining the gold standard of service as being the family doctor visit, so that the implications of the opt out choice are clearly understood. Future studies of interventions that provide information may wish to provide more than two options, although this makes the survey more complex for both the respondent and researcher.

The selection of attributes and levels is a critical component of any DCE. It is possible that different attributes and levels should have been included. Perhaps a focus group with other HCPs, such as family doctors or pharmacists, might have served to further inform the decisions made about the attributes and levels. The evaluation is limited to the attributes and levels that were selected.

Overall, respondents demonstrated logical and consistent decision making. It is possible that respondents grew fatigued through the survey, as failures in the best-worst task increased when it was repeated towards the end of the survey. Respondents who failed the best-worst task were younger and less educated; a previous study also found that younger respondents were more likely to fail a validity test [227]. While these respondents did not have an impact on the overall results, it is important in future to establish appropriate decision rules for handling illogical decision makers. Perhaps a threshold level could be established for which a change in the beta estimate is considered significant enough for the illogical decision makers to be modeled separately; for example, if the beta increases or decreases by 20% the illogical decision makers should be removed from the overall analysis. Their responses, however, should still be considered since as previously discussed they may not necessarily be illogical but perhaps possess unique preferences or decision-making heuristics.

### 3.5 Conclusions

The DCE found that receiving very helpful information is the most important feature of teratology counseling, and that the methods by which information is delivered are less important. Characteristics common to both TIS and physicians were felt to be important, and overall it is difficult to determine which service model may be most preferred as the influence of the quality of information attribute was so large, it may outweigh any other service features. The findings are limited by the attributes and levels selected for evaluation, and to the scenario of an anti-depressant exposure during pregnancy. The findings may not be generalizable to other populations as this sample was largely female, educated, and urban. Preferences may not be generalizable to other types of exposure inquiries. Currently, no cost-effectiveness data for this type of counseling exists. The robustness of WTP values above \$90 is unknown. All WTP values have not been validated in real life settings. DCEs are a valuable tool in performing program

evaluations in contexts where health outcomes are difficult to quantify, and utility may be affected by the process of care.

## 4 Chapter 4: Methodological Challenges in Using Willingness-to-Pay Estimates in a Cost-Benefit Analysis of a Teratology Counseling Encounter

### 4.1 Introduction

#### 4.1.1 Overview of Cost-Benefit Analysis

A cost-benefit analysis (CBA) compares the costs of a given program or intervention with its benefits, measured in dollar terms. The measurement of health benefits in dollar terms rather than change in health status is what distinguishes a CBA from cost-effectiveness and cost-utility analyses (CEA and CUA, respectively) [97]. While CBAs had historically not achieved the popularity of CEA or CUA in health economic evaluations, recent years have seen an increase in the use of CBAs in addressing a myriad of policy and funding issues [171]. An advantage of CBA over CEA and CUA is that comparisons can be made to non-health programs when such analyses are being used to inform resource allocation. As well, CBA may be better able than CEA and CUA to capture the value of non-health outcomes such as reassurance, and spillover effects to other individuals, as CEA and CUA are generally more narrowly focused on an individual patient [97, 319].

Given that CBAs are less commonly performed, few methodological guidelines are currently in place, providing many challenges when this framework is used. This chapter presents an example of a CBA for a single teratology counseling encounter regarding anti-depressant use during pregnancy. Costs and benefits of a counseling intervention that provides teratology information were estimated, with benefits measured by WTP values generated from a DCE (see chapter three). The benefit being assessed is the benefit to a user of a teratology information consultation on the use of an anti-depressant during pregnancy, rather than an improvement in a particular health outcome or benefits accrued to society through the provision of such a program.

An understanding of welfare economics is important to understanding the estimation of benefits. Welfare economics is a branch of economics that deals with the valuation of social welfare. Two key concepts of welfare economics, termed the Pareto principles after the economist Vilfredo Pareto, are that social welfare is comprised of the welfare of each individual in society, and that individuals are the best judges of their own welfare [97]. Economic evaluations that include

elicitation of consumer preferences, including DCEs, are therefore rooted in the principles of welfare economics [313, 320]. The definition of what individuals are being asked to pay for is an important aspect of WTP. Goods may be private, where benefits accrue only to the individual who pays for them (e.g. orthotic shoe inserts) or public, where people receive benefits whether they pay for them or not (e.g. an immunization program) [183]. To value a public good, individual WTP are added, as each unit of good or service is equally shared by all [183]. This may be problematic if individuals consider benefits to others in their consideration of a benefit that is intended by the researcher to apply only to them. The unit of analysis in this study was a one-time consultation, with benefits accruing to one individual.

The cost and benefit inputs each have variability and uncertainty. To address the uncertainty in the estimates, a probabilistic sensitivity analysis (PSA) comprised of Monte Carlo simulations was used to analyze the data. The PSA can not account for errors in measurement, that is, if the DCE used to estimate the WTP values was mis-specified, or if relevant cost items were left out, such errors will not be captured in the PSA. The total WTP estimates were based on an aggregation of WTP values for particular service attributes. A secondary analysis was conducted where WTP was reduced because there was uncertainty about the specification of one of the service attributes; specifically, it was not certain that a user would have confidence in the TIS and so the WTP was reduced by the corresponding amount of benefit gained by having confidence in the IP. The analysis was first conducted from the societal perspective, where service provision costs were included as well as productivity costs to the user. Another analysis was then conducted from the health care payer perspective, where only service provision costs were included. Methodological challenges with respect to the measurement of costs and benefits and their use in a CBA will be identified and discussed.

#### 4.1.2 Rationale

An economic evaluation comparing costs and benefits of teratology counseling by TIS and family doctors has not yet been conducted. CBA was used as the evaluation framework, with benefits measured in dollar terms using willingness-to-pay derived from a discrete choice experiment (see chapter three). Measuring the benefits of a teratology counseling encounter presents a challenge. SP methods allow for the estimation of benefits in a hypothetical situation. While the hypothetical nature of these methods is a limitation, they may be more appropriate for

valuing a counseling intervention than an RP method or via quantification of changes in health outcomes. RP methods are not possible because no market exists for these services, and evaluating changes in health outcomes may not be comprehensive enough for a counseling intervention. CBAs are not often conducted in health care; using WTP values as the measure of benefit in a CBA is rare as well. An example of such a study will be useful for demonstrating the methodological challenges for this analysis framework. There are many limitations and uncertainty in the estimation of costs and benefits used in the analysis, and the feasibility of addressing some of this uncertainty by using PSA needs to be explored.

### 4.1.3 Objectives

The objective was to compare the costs and benefits of a TIS and physician encounter in an incremental analysis to determine the probability that the incremental benefits of TIS exceed costs for a single counseling consultation about using an anti-depressant during pregnancy.

## 4.2 Methods

### 4.2.1 Overview of Methodological Challenges

There are two main areas of challenge in this CBA. The first is the monetarization of benefits using WTP values derived from a DCE. It is possible that benefits were measured incorrectly. The DCE provides utilities for individual levels of potential attributes of a service. Service scenarios are described by levels, and the utilities for each level are aggregated to provide a total utility for a service scenario. The utility is then divided by the marginal utility of money to derive WTP for that service scenario.

The measurement of benefits is dependant on the correct specification of the DCE. It is possible that the DCE was mis-specified. Measurement errors may have been made if utilities were elicited inappropriately or the service scenarios were inaccurate. For example, were all important attributes included, described the right way, and assigned the appropriate levels? There is no method of addressing inappropriately elicited utilities at this point. Every effort was made to include all appropriate attributes and levels and to describe them correctly (see chapter three).

To account for possible variations in the service scenarios, two approaches were taken to specifying the TIS scenario descriptions. The appropriate method for estimating variance of the

WTP values is unknown. A bootstrap approach was used, providing an estimate of variance for use in the PSA. These challenges will be discussed further in the section describing the measurement of benefits.

The second main challenge in this area is more specific to the subject area, yet common to many economic evaluations. That is, appropriately estimating costs for the TIS intervention. Telephone counseling is one aspect of the service provided by TIS. Costs are highly variable depending on the service setting, staff, and responsibilities. Appropriate measurement of costs was a challenge, and will be described in the measurement of costs section.

## 4.2.2 Cost-Benefit Analysis

An incremental CBA was performed comparing the net benefit (NB) of TIS and physician services (assumed to be the alternative to TIS; refer to chapter three for the rationale of the selection of physician services as the service comparator). The NB is the difference between the costs and benefits of an intervention. The benefits were measured via WTP for a consultation following an exposure to anti-depressants in early pregnancy, with WTP values derived from a previously conducted DCE where cost was included as an attribute. The NB was estimated for an individual consultation. Additional distal costs and benefits that may occur as a consequence of teratology counseling, such as the treatment of depression, counseling other HCPs and producing research, were not included in the analysis.

### 4.2.2.1 Time Horizon

The time horizon was limited to one consultation. Future service use and outcomes following use were not evaluated so it was unnecessary to perform discounting of the costs and benefits.

### 4.2.2.2 Perspective and Costs

In order to provide the most comprehensive and accurate description of costs, a limited societal perspective was adopted [97]. Under the limited societal perspective, both service-related and user productivity costs were included. Service costs associated with counseling on anti-depressant use in pregnancy could include physician time and diagnostic ultrasounds to detect malformations. In this evaluation, service costs incurred following the counseling intervention were assumed to have the same patterns for both TIS and physician users, therefore only the

costs of service delivery were evaluated, which is a potential limitation. Productivity costs are those costs associated with missed time from work or other activities by patients and/or caregivers due to a person's health condition. Travel costs were not modeled as these are too variable to predict accurately. This is a potential limitation of the analysis, as physician costs may be underestimated. Please refer to Table 45 for a full summary of the estimates and distributions used in the analysis. A second analysis was conducted from the health care payer's perspective, that is, productivity costs were not included.

#### 4.2.2.3 Incremental Comparison of Net Benefit

The net benefit (NB) is the difference between program costs and program benefits, both valued in monetary terms, as represented by the following formula:

$$\text{NB} = (\text{Benefits}) - (\text{Costs})$$

The benefits and costs were calculated for both TIS and physician services. The difference in costs and the difference in benefits between the two services were then calculated to provide the incremental NB (INB) of TIS, according to the following formula:

$$\text{INB} = (\text{Benefits}_{\text{TIS}} - \text{Benefits}_{\text{Family Doctor}}) - (\text{Costs}_{\text{TIS}} - \text{Costs}_{\text{Family Doctor}})$$

An incremental analysis allows one to determine whether the additional benefits observed with an intervention exceed any additional costs compared to a standard intervention.

### 4.2.3 Measurement of Benefits

#### 4.2.3.1 Derivation of Willingness-to-Pay from a Discrete Choice Experiment

A DCE was conducted to estimate preferences and WTP for teratology counseling (see chapter three). In the survey, men and women (adults 18-65 years of age) from a cross-section of society were recruited and all were asked to imagine that they or their partner were newly pregnant and wanted more information about using an anti-depressant medication during pregnancy. Users of the Motherisk program were not excluded. Motherisk users represented 19% of survey respondents, and indeed were found to have slightly different preferences than the rest of the study sample (see chapter three). Only surveying Motherisk users or pregnant women would not

lead to a true estimate of the public value of these services. It is possible that people with a vested interest in a certain program may value it more highly than people who do not regularly use it or may not ever use it.

As described in chapter three, the attributes that were evaluated in the survey were generated through examinations of the literature, consideration of the key differences between TIS and family doctor teratology counseling, and focus group discussions. It is possible that the attributes and levels selected were inappropriate; however every effort was made to design the survey in a rigorous and appropriate fashion. If there were errors in the description of attributes and levels or in the survey design, it will affect the measurement of benefit in the economic evaluation.

The WTP approach for individual consumption is the most conservative estimate of benefits. There are spillover benefits to other persons that may be taken into account when WTP values are being elicited from an individual. This may occur if the survey respondent considered spillover effects in their WTP estimation. For example, a spillover effect of pregnancy information may be that the quality of life for other family members is improved due to decreased stress in the recipient of the information. No attributes, however, were included in the DCE that suggested the respondent explicitly consider spillover effects. It is possible that respondents considered spillover effects themselves, although the extent to which this occurred on an individual level is unknown.

Estimating WTP values from DCEs is still a method in progress. Studies of internal validity of DCEs have generally found good internal validity, i.e. they consistently measure people's preferences [168, 313]. Whether people's stated WTP values as generated by DCEs reflect what people would actually do in real life is more difficult to assess [321, 322]. Reasonably good correlation between stated and actual WTP in health care settings and in donations to environmental causes has been found, demonstrating criterion validity, which means that WTP values matched an external criterion [322, 323]. Another method to determining if stated preferences correspond to actual preferences is to assess convergent validity, that is, if WTP values in one study for one good are similar to WTP values for a similar good in another study. Convergent validity has been demonstrated in empirical evaluations of DCEs [324]. Determining whether stated preferences for hypothetical scenarios are a reasonable reflection of actual

behaviour remains one of the main limitations to using WTP data in a full program evaluation. This may be particularly difficult to validate in publicly funded health care systems.

The logit regression analysis of the DCE data provided WTP values for attributes of a teratology counseling consultation (Table 41). The beta estimates are from the full model including all significant interaction terms, which are not shown. The WTP values are generated by dividing the beta estimates by the marginal utility of money, which is based on the beta estimates for the cost attributes, which are not shown (see chapter three). Bootstrapping methods were used to generate 95% CIs. As previously discussed in chapter three, it is possible that a unit change in the attribute level does not have an equal effect on marginal utilities; for example, paying \$100 more for a good is the same marginal difference if you pay \$300 rather than \$200, but this may be perceived as being worse than paying \$200 rather than \$100. The linear additive model is assumed for most choice models, and other types of models have not shown significant improvements in model fit [214, 278]. For this reason it was decided to use all data points to calculate the marginal utility of money rather than the last two (\$50, \$90), even though the difference between \$10 and \$50 may be different from the difference between \$50 and \$90. As modeling research has not developed reasonable alternative models it was decided to assume linearity and use all data points available.

**Table 41: Willingness-to-Pay for Service Attributes**

Attribute (level)	Beta Estimate	WTP (\$)			Reference Level (Beta=0)
		Point Estimate	Lower 95% CI	Upper 95% CI	
Training (Counselor)	0.133	11	6	16	Family physician
Method (Telephone)	0.231	19	13	26	In-person appointment
Knowing (IP is known)	0.528	43	36	54	IP is not known
Confidence (Have confidence in IP)	0.433	35	26	45	Unaware of skills of IP
Helpfulness (Info. is very helpful)	0.717	59	48	74	Info. is somewhat helpful

IP=Information Provider; CI=Confidence interval

#### 4.2.3.2 Willingness to Pay for TIS

There were two approaches used to calculate WTP for TIS. The first approach was based on the configuration of service levels shown in Table 42, which represent TIS features.

**Table 42: Levels and Willingness-to-Pay for TIS in First Approach**

Level	WTP (\$)		
	Point Estimate	Lower 95% CI	Upper 95% CI
Training=Counselor	11	6	16
Method=Telephone	19	13	26
Knowing IP= Not known	0	0	0
Confidence= Have confidence in IP	35	26	45
Helpfulness=Info. is very helpful	59	48	74
<b>Total</b>	<b>124</b>	<b>93</b>	<b>162</b>

IP=Information provider; CI=Confidence interval; WTP=Willingness-to-pay

The first two (training of IP and method of contact) are inherent characteristics of TIS. It was assumed that the IP is not known to the TIS user. Therefore a zero amount was assigned for this level, as utility was gained when the IP was known and not knowing is the zero utility reference level. It was assumed that the information would be very helpful based on previous literature. As doctors often use TIS as a resource it was assumed that TIS have high quality information [85]. Surveys have also shown that doctors themselves rate the quality of TIS information as very high [87]. Total WTP for TIS in the first approach exceeded \$90, which was the highest price level set in the DCE. The slope of the marginal utility of money past the \$90 point was unknown and was assumed to be linear; it is possible, however, that the relationship is not linear. Since a level of WTP as high as this aggregate WTP value was not included in the survey, it is possible that the calculated aggregate WTP is higher than the true WTP and may therefore not be robust. The total WTP for TIS was less than \$90 in the second approach (described below). Although \$90 was the highest value presented in the survey, presumably the service scenarios being presented were not optimal (that is, did not contain all the preferred levels). The TIS scenario in the first approach has almost all the most preferred levels, therefore it is possible that WTP is higher than \$90 when the scenario is almost optimal. It has been previously observed that aggregate WTP for optimal scenarios is higher than the ceiling price provided in the survey (see section 4.4.2.2 for a further discussion of this issue) and this threat to validity warrants further research.

In the first approach it was assumed for both TIS and the family doctor visit that the user would have confidence in their skills. In the second approach it was assumed that the user would not be confident in the TIS, with the corresponding levels and WTP shown in Table 43.

**Table 43: Levels and Willingness-to-Pay for TIS in Second Approach**

Level	WTP (\$)		
	Point Estimate	Lower 95% CI	Upper 95% CI
Training=Counselor	11	6	16
Method=Telephone	19	13	26
Knowing IP= Not known	0	0	0
Confidence= Do not have confidence in IP	0	0	0
Helpfulness=Info. is very helpful	59	48	74
<b>Total</b>	<b>88</b>	<b>67</b>	<b>117</b>

IP=Information provider; CI=Confidence interval; WTP=Willingness-to-pay

#### 4.2.3.3 Willingness to Pay for Family Doctor Visit

WTP for a family doctor visit was based on the configuration of service levels shown in Table 44, which exemplify counseling provided with a physician visit.

**Table 44: Levels and Willingness-to-Pay for Family Doctor Visit**

Level	WTP (\$)		
	Point Estimate	Lower 95% CI	Upper 95% CI
Training=Family Doctor	0	0	0
Method=Appointment	0	0	0
Knowing IP= Known	43	36	54
Confidence= Have confidence in IP	35	26	45
Helpfulness=Info. is somewhat helpful	0	0	0
<b>Total</b>	<b>79</b>	<b>62</b>	<b>99</b>

IP=Information provider; CI=Confidence interval; WTP=Willingness-to-pay

Utility is gained when the user speaks with a specialized counselor over the telephone (as these were the preferred levels in the DCE), therefore these levels (family doctor and appointment) are set to the zero value reference level. It was assumed that the user would know the IP as they are their family doctor, therefore this service scenario has a utility gain on that level. As described previously, it was assumed that the user would have confidence in family doctor services. The assumption that physician services would provide somewhat helpful information was based on previous surveys, which have collectively indicated that TIS are highly utilized by physicians and that some physicians lack confidence in areas in which TIS are specialized [77, 85-87].

#### 4.2.3.4 Summary of Measurement of Benefits and Methodological Challenges

The monetarization of benefits using the WTP values is dependent on how the DCE survey was designed. It is possible that there were errors in the design, however the instrument was developed in a rigorous manner using focus groups and field testing. The assumptions used to design the service scenarios were described. It is possible that the service scenarios were not assigned the appropriate levels. This was examined by taking two approaches to estimating TIS benefits. Some studies have shown WTP values elicited by DCEs to be internally and externally valid, yet further research is needed [168, 313, 322-324]. Uncertainty in WTP values will be accounted for in the PSA by using CIs generated by bootstrapping.

#### 4.2.4 Measurement of Costs for TIS

Few data are available regarding the cost of providing TIS. TIS vary in terms of size, number of telephone counselors, training of the telephone counselor, functions and goals (e.g. some TIS perform research and some do not), and are also subject to variation based on their geographic location (e.g. salary and overhead costs in smaller cities may be lower than in urban areas). TIS are also integrated into other services to varying degrees. For instance, some TIS are unique stand-alone facilities whereas others are housed within a hospital department that provides a host of pregnancy-related services. The location of the service may also affect cost items such as salaries (e.g. a research hospital-based professional may offer higher salaries than an individual clinic). For these reasons, estimating the cost of one consultation was a challenge. The budget data provided by TIS (see chapter two) was highly variable and made up of disparate cost items. For example, some budgets included salaries, research and travel costs whereas others did not. It was also unknown whether the five TIS that did not provide a budget were different from the other TIS, and therefore using the value based only on the TIS budgets available might introduce bias and not be representative of true costs. For these reasons it was decided that the TIS consultation would be micro-costed. A description of the costing process follows.

The survey described in chapter two provides the best description of current TIS costs. These data were used to inform the costing of TIS along with other publicly available information. An estimate of the cost of one person providing one consultation was desired for both interventions (TIS and family doctor). Four inputs were used to determine the cost per consultation: 1) the

salary of the telephone counselor (Stc), 2) the salary of an administrative worker (Sa), 3) the overhead costs of providing the telephone service (O), and 4) the time it takes to complete a consultation (T). The three cost estimates were calculated in a per hour format. These values were added to determine the TIS counseling cost per hour and then multiplied by the time required for the consultation as per the following formula:

$$\text{TIS cost per consultation} = (\text{Stc} + \text{Sa} + \text{O}) * \text{T}$$

The estimation of each of these variables is described below.

#### 4.2.4.1 Salary of Telephone Counselor

The salary of a TIS telephone counselor is not generally available from outside sources, as this is a unique position. The survey of TIS did not explicitly ask for counselor salaries, which was a limitation of the survey design. In the U.S., telephone counseling is often performed by genetic counselors (GCs). A GC is a certified professional who has received a master's degree. Although TIS telephone counselors vary in their training and backgrounds, it can be argued that their skill set is similar to that of a GC, in that they will have had training in the sciences and in counseling and will likely have an advanced degree. What is important to assess is the opportunity cost to society by having someone with this skill set perform teratogen counseling rather than perform another job. Therefore, salary estimates for genetic counselors were used as proxies for salaries of telephone counselors. Salary data were obtained from a website that specializes in reporting salary estimates for various professionals in the U.S. The website reported a median annual salary of \$58,184, plus 10<sup>th</sup> and 90<sup>th</sup> percentile salaries, in 2009 US dollars [325]. The website also provided estimates of costs of bonuses, social security, 401k/403b, disability, health care, pension and time off, bringing the total median salary to \$81,848. These values were converted into an hourly rate by dividing them by 1820 (35 hours per week\*52 weeks per year). All costs were converted into 2008 Canadian dollars using the Bank of Canada average annual exchange rate and the StatsCan consumer price index [110, 326]. The mean hourly wage in 2008 Canadian dollars was \$47.19 (SD 6.2).

#### 4.2.4.2 Salary of Administrative Support Workers

Administrative workers are needed to support almost any service. The cost per hour of providing administrative support to TIS was determined by examining the survey of TIS. Not all TIS

reported using administrative support workers; reasons for this are unknown. It is possible that the counselor themselves performs administrative duties, or they are supported by administrative staff in another department.

It was difficult to estimate how much administrative time is required to support TIS consultations because of the variation in how the services are operated, as described in the introduction to this section. The TIS who reported FTEs for administrative staff (n=9) had also reported what percentage of their services' time was spent performing telephone counseling (Ptc). This percentage was applied to the number of administrative FTEs (AdFTEtotal) determine the amount of administrative work devoted to supporting counseling (AdFTEtc). Administrative tasks that support counseling could include creating and filing consultation data forms, data entry, and other miscellaneous office duties. The number of administrative FTEs was divided by the number of counseling FTEs (FTEtc), so that the number of administrative FTEs per counselor FTE was estimated, according to the following formulae:

$$\mathbf{AdFTEtc = (Ptc) * (AdFTEtotal)}$$

$$\mathbf{Administrative\ FTEs\ per\ counselor\ FTE = (AdFTEtc) / (FTEtc)}$$

The median value (0.16 administrative FTEs per counselor FTE) was applied to the hourly wage for administrative workers obtained from the same salary source used for the GC salaries [325]. While this was a rough estimation, it seems reasonable to expect that for one counselor working full time, 0.16 FTEs of administrative work (which works out to 5.6 hours per week) would be required. This results in a mean hourly cost of \$4.89 (SD 0.81).

#### 4.2.4.3 Overhead Costs

The cost items included in the budgets for the 13 North American TIS with budget data were examined. Two TIS provided only the cost of administering the service (i.e. no salary or research costs were included in the budgets). For one TIS, the cost items included were equipment and supplies, telephone lines, postage, and database access. For the other TIS, the cost items included were equipment and supplies, telephone lines, database access, conference travel, library services, journal subscription, insurance liability, postage, printing, promotion and consultant fees. These budgets were used to determine an estimate of overhead costs per hour of consultation at TIS.

To allocate overhead costs, the number of counseling hours worked at the TIS was determined by taking the number of counseling FTEs and multiplying that by 1820 (35 hours per week \* 52 weeks per year). The total annual budget was then divided by the number of counseling hours. This yielded an estimate of the overhead cost per counseling hour at TIS (range \$7-15 per hour). The overhead cost per hour includes some costs above what may be required (e.g. consultant fees) and may be an overestimation.

Overhead costs for rent and utilities other than telephone lines were not included in these cost estimations. This is a potential limitation of the study. However, most TIS require very little space to operate (for the 16 TIS that reported their office space square footage, the median was 360 square feet). Most TIS noted in the survey that their office space is shared with other services, and some counselors may even work from their homes. Another limitation to the analysis is the cost of the time spent by the telephone counselor being trained and potentially preparing statements regarding specific medications. This is likely a large initial investment of time, depending on the existing expertise of the telephone counselor, yet may be minimal on an ongoing basis. This cost has not been estimated which is another possible limitation of the study.

#### **4.2.4.4 Time to Complete a Consultation**

The above calculations provide the components of the cost per counseling hour for TIS. The cost per consultation can then be determined based on the time it takes to complete an average consultation. It was assumed that calling a TIS with this type of inquiry would take thirty minutes, consisting of telephone counseling time and documentation time. This is based on the survey of TIS which found that the mean call duration was 15 minutes with a standard deviation of 13.11 minutes [190]. The total time was rounded up to thirty minutes to allow for 15 minutes of documentation time. A minimum total value of 15 minutes was estimated, and a maximum of one hour (which was the maximum time provided in the TIS survey).

#### **4.2.4.5 Using These Inputs to Determine the Cost per Consultation**

The three cost inputs were added to get a cost per hour for a TIS consultation, and then multiplied by the time per consultation. Please refer to Table 45 for a full description of the costs and their distributions.

#### 4.2.4.6 TIS Productivity Costs

In the DCE questionnaire, respondents were instructed not to consider other out-of-pocket costs such as travel costs and lost productivity in order to avoid double-counting (Appendix 11). Double-counting may occur if individuals consider productivity or travel costs in their valuation of the intervention, which the researcher may estimate themselves and add in separately as a cost item. It was estimated that calling a TIS would take approximately 30 minutes of the caller's time, with approximately 15 minutes for the counseling (as per the TIS survey) and 15 minutes allocated to looking up the number and being placed on hold. Average wages were obtained from the Statistics Canada 2009 Census, which found that the average hourly wage for a woman aged 25-54 years employed full time was \$23.10 in 2008 [297]. The range for time was from 15 minutes (the counseling time without being on hold) to up to two hours. The maximum time for a call reported in the TIS survey was one hour. An additional hour was assigned for finding the TIS and being placed on hold.

#### 4.2.5 Measurement of Costs for Physician Services

##### 4.2.5.1 Family Doctor Operational Costs

The cost of consulting a physician for teratology counseling regarding anti-depressant use during pregnancy was assumed to be equivalent to a physician visit. The cost of a visit to a family physician was obtained from fee-for-service codes in the Ontario Health Insurance Plan (OHIP) fee schedule (Ontario Ministry of Health and Long-Term Care) [200]. As billing practices may vary and depend on whether a special visit is made or if the pregnancy exposure counseling is part of an overall consultation, different costs were assessed. The cost for an intermediate assessment by a family physician (code A007), is CDN \$31.95. The fee for a minor assessment (A001, CDN \$17.75) or the fee for a consultation (C005, CDN \$56.10) are also feasible costs, and all were evaluated in the CBA (see Table 45). As physicians use billings to cover overhead and administrative costs, no additional costs were added.

##### 4.2.5.2 Family Doctor Productivity Costs

It was assumed that patients visiting a physician incur productivity losses to attend the appointment. Productivity losses due to time away from work or usual activities associated with visiting a doctor's office were based on reasonable assumptions regarding patient behaviour and

previous research. It was estimated that a visit to a doctor's office results in two hours of lost productivity, with a range from 0.5 to three hours [150, 152]. Productivity losses were estimated using the same methodology as for TIS (StatsCan 2009 Census) [297].

#### 4.2.6 Data Analysis and Probabilistic Sensitivity Analysis

As previously mentioned, as the data were uncertain, a PSA using Monte Carlo simulation was performed. Monte Carlo simulations randomly sample data repeatedly from a specified range and distribution for each variable in order to better understand the ranges of possible outcomes given uncertain data. In this analysis, costs and benefits were described in terms of central tendencies, ranges, and distributions. One thousand replications were conducted. The Monte Carlo simulation was conducted using Oracle Crystal Ball® software, which is an add-on to the Microsoft Excel® program [327].

The program asks the user to enter the base value of a variable of interest. It then asks the user to define the distribution of this variable. There are 22 potential distributions in the program. A basic distribution is the normal distribution, shaped like a bell curve, in which the user must enter the mean and SD for the variable of interest. This distribution was assigned to the WTP estimates and to the salary data used to estimate direct TIS costs. Another distribution is the triangle distribution, which is commonly used when the user only knows the minimum, maximum, and most likely values. Another distribution is "uniform", which means that the researcher has no knowledge about the distribution and therefore each value in the range is equally likely to be drawn for the simulation. The overhead cost per hour distribution was set as uniform as this estimate was based on two data points and information about distribution was not known. A custom designed modal distribution was used for the family doctor billing code. Similarly to the uniform distribution, it was unknown with what frequency a doctor might use one of the three different billing codes related to a consultation. However, unlike a uniform distribution where any value between the maximum and minimum value may be selected with equal probability, there were only three possible values. Therefore the modal distribution was custom designed so that each of the three values had a 0.33 probability of being selected. The variables used in the PSA are presented in Table 45.

**Table 45: Variables and Ranges Used in the Probabilistic Sensitivity Analysis**

<b>Variable explanation</b>	<b>Variable label</b>	<b>Base Case Value (\$)</b>	<b>Range (\$)</b>	<b>Distribution</b>	<b>Source</b>
<b>BENEFITS</b>					
WTP for TIS	Bt	124	93-162* (SD 12)	Normal	DCE; bootstrapped data
WTP for family doctor	Bf	79	62-99* (SD 8)	Normal	DCE; bootstrapped data
<b>COSTS</b>					
<i>Direct TIS Costs</i>					
Counselor salary cost per hour	Stc	47.2	42-57** (SD 6.2)	Normal	GC salary from salarywizard.com
Administrator salary cost per hour	Sa	4.9	4-6 (SD 0.8)**	Normal	TIS survey for time; salary from salarywizard.com
Overhead cost per hour	O	NA	6.9-14.7 <sup>+</sup>	Equal	TIS survey
Time per consultation (hours)	T	0.5	0.25-1.0 <sup>+</sup>	Triangle	TIS survey
<i>Indirect TIS Costs</i>					
Productivity cost	Pt	12	6-46 <sup>+</sup>	Triangle	TIS survey for amount of time; StatsCan 2009 census for wages
<i>Direct Family Doctor Costs</i>					
Cost per family doctor visit	Cf	NA	18-56 <sup>+</sup>	Modal	OHIP billing codes
<i>Indirect Family Doctor Costs</i>					
Productivity cost	Pf	46	12-69 <sup>+</sup>	Triangle	Telehealth surveys for amount of time; StatsCan 2009 census for wages

NA=Not applicable

\*95% Confidence Interval

\*\*90% Confidence Interval

<sup>+</sup>Minimum-Maximum Range

Once the distributions have been set and the variables defined, the simulation is run. The calculation of the INB was performed 1000 times, in each run drawing a number from the potential range, with the probability of a number being drawn dependent on the defined distribution. The INB of TIS was calculated according to the following formula:

$$\text{INB} = ( \text{Bt} - \text{Bf} ) - [ ( ( ( \text{Stc} + \text{Sa} + \text{O} ) * \text{T} ) + \text{Pt} ) - ( \text{Cf} + \text{Pf} ) ]$$

#### 4.2.7 Two Approaches to Estimating TIS Benefits: Model Uncertainty

It was initially decided that both TIS and family physician services would have the level for the confidence attribute be set to “have confidence in the skills of the information provider.” However, it is likely that there are scenarios in which the reputation of TIS is unknown to the user and they may not have confidence in them. There are many types of uncertainty in an economic evaluation [328]. We have termed this problem model uncertainty, in that we are uncertain about the levels that will describe the service scenario. This goes beyond a multi-way sensitivity analysis, whose results would have been elucidated in the primary PSA, but is a re-definition of the service scenario. The PSA accounts for variability in the chosen inputs, however it is not possible to account for the potential re-configuration of levels in a PSA as this is a variation based on the definition of the service scenario.

#### 4.2.8 Analysis from the Health Care System Perspective

In the primary analysis, a limited societal perspective was adopted and productivity costs were included. To conduct an analysis from a health care system perspective, productivity costs were removed and the CBA was conducted without these cost inputs (i.e. Pt and Pf were not included in the incremental NSB equation).

##### 4.2.8.1 Health Care System Perspective with Model Uncertainty

Similarly to the primary analysis, the analysis from the health care system perspective was also conducted with a reduced WTP for TIS after removing the gain in utility achieved from having confidence in the IP.

### 4.3 Results

#### 4.3.1 Results of the Probabilistic Sensitivity Analysis

The results of the PSA are presented in Table 46. The probability that the incremental NSB for TIS is positive is 99.1%, signifying that incremental benefits exceed incremental costs when compared to a family doctor visit. On average, \$63 would be saved if counseling occurred via a TIS rather than a family doctor visit.

**Table 46: Results of Probabilistic Sensitivity Analysis: Approach One, Productivity Costs Included**

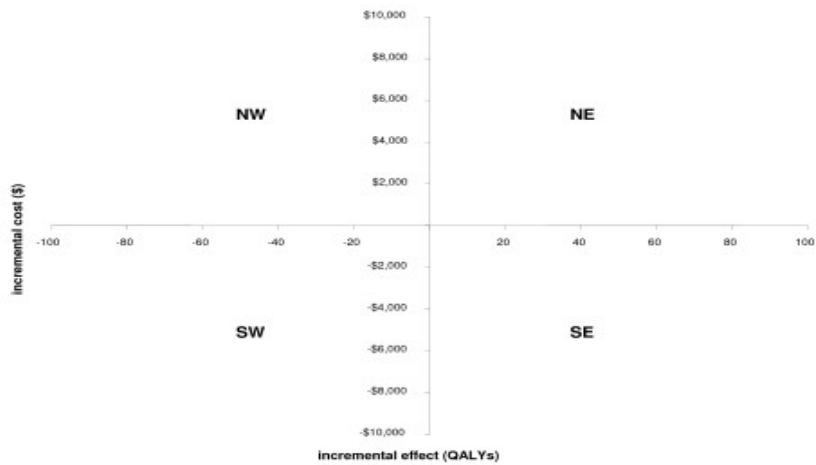
	<b>Mean (\$)</b>	<b>SD (\$)</b>	<b>Median (\$)</b>	<b>Minimum (\$)</b>	<b>Maximum (\$)</b>	<b>Probability that value is greater than zero (%)</b>
Incremental Benefits	44	14	44	-5	97	99.7
Incremental Costs	-19	24	-20	-83	50	21.9
(Incremental Benefits)- (Incremental Costs)	63	28	63	-20	159	99.1

SD=Standard deviation

These results are logical as in most circumstances WTP for TIS was higher than WTP for a family doctor consultation, and productivity costs were also higher for a family doctor visit, meaning that the difference in costs was negative.

These results can also be visualized graphically. The cost-effectiveness plane is commonly used in incremental CEA to demonstrate the differences in costs and effects between two interventions [97]. The difference in effects is plotted on the x-axis and the difference in costs is plotted on the y-axis. If incremental costs are positive, i.e. the intervention costs more than the status quo, then the cost will be in one of the northern quadrants. If the effects gain is positive, i.e. the intervention has greater health effects, then the effects will be in one of the eastern quadrants. Many interventions commonly fall into the North-Eastern quadrant, that is, incremental costs are higher and incremental effects are higher. When an intervention falls into this quadrant, trade-offs must be made. The other quadrants are simpler to interpret. Please refer to Figure 6 for an example of the incremental cost-effectiveness plane.

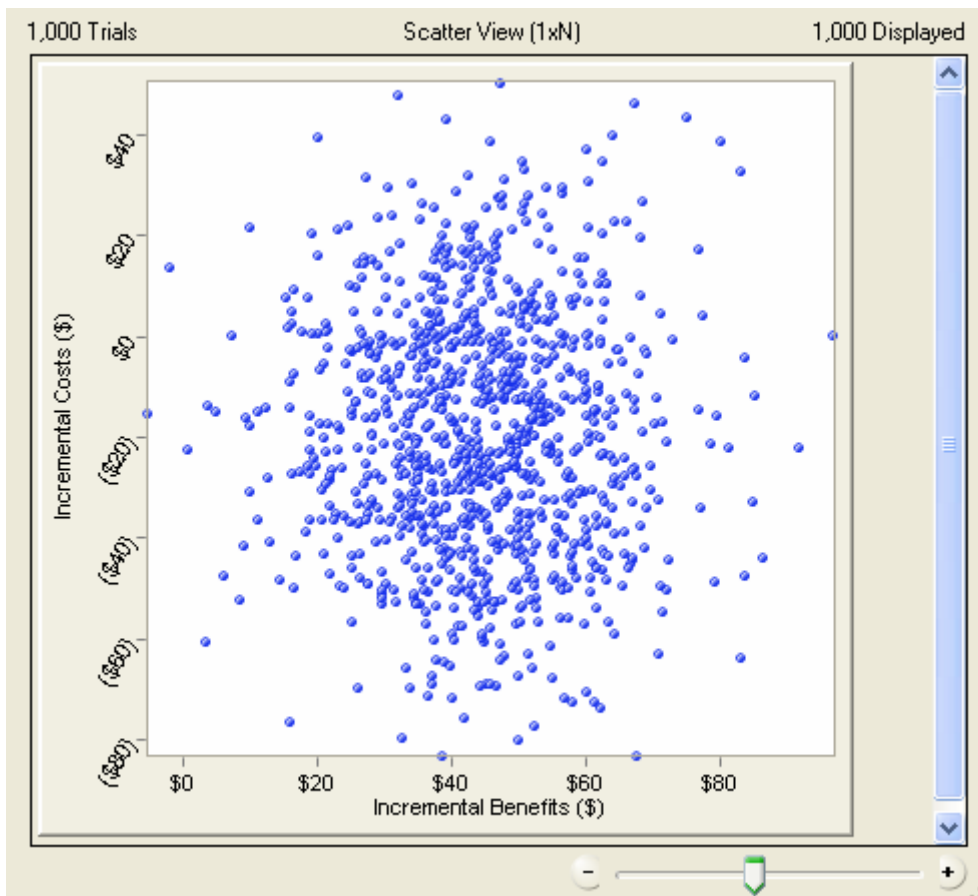
**Figure 6: The Incremental Cost-Effectiveness Plane**



The incremental cost-effectiveness plane. NE = northeast quadrant; NW = northwest quadrant; SE = southeast quadrant; SW = southwest quadrant; QALY = quality adjusted life year. Adapted from Fenwick et al. BMC Health Services Research. 2006; 6:52 [329].

The cost-effectiveness plane was modified so that rather than effects on the x-axis, the difference in benefits was plotted. As can be seen in Figure 7, benefits were generally higher and costs lower for the intervention, as most of the dots appear in the South-East quadrant.

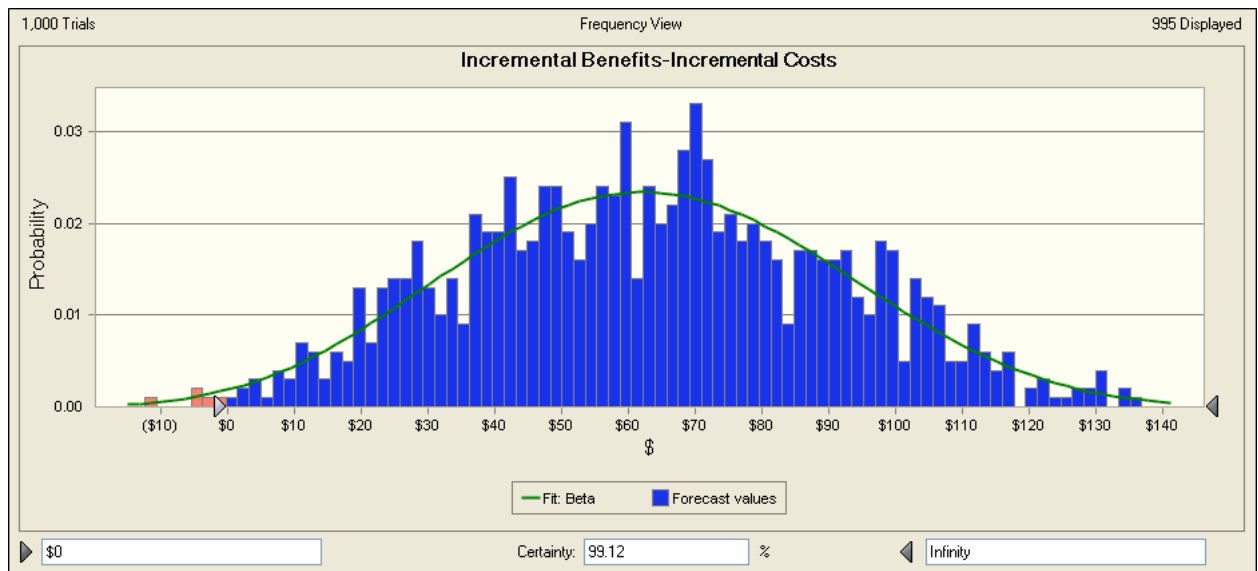
**Figure 7: Scatter Plot of Incremental Costs and Incremental Benefits Plotted in Cost-Benefit Plane**



(Negative values in brackets)

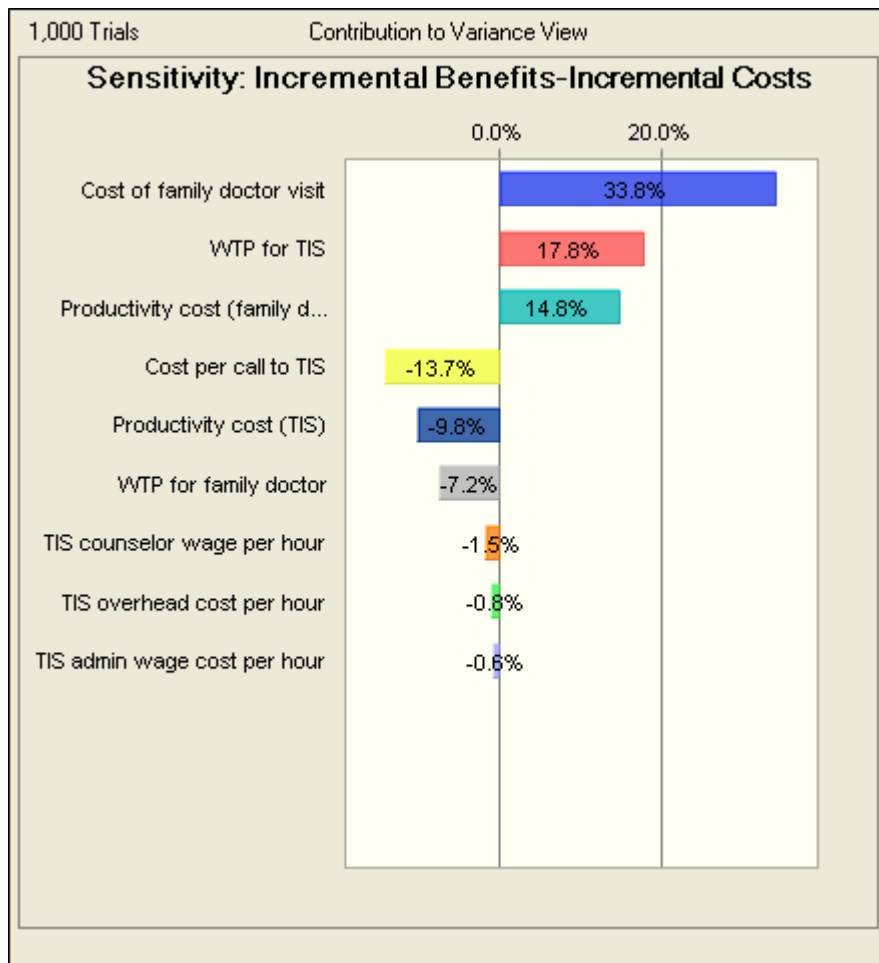
Another way to visualize the results of the base case analysis is in a histogram. The histogram shows the probability of the INB being negative. As can be seen in Figure 8, the probability of the INB being less than zero is very small (<2%). See Appendix 12 for the distributions of incremental benefits and incremental costs.

**Figure 8: Histogram of Incremental Net Benefit**



The sensitivity analysis chart in Figure 9 shows the influence of each variable on the INB. The variables that are positive contribute towards the incremental NSB being positive, and vice versa for the negative variables. The main contributor to the variance in this analysis was the cost of the family doctor (33.8%), followed by the WTP for TIS (17.8%) and the productivity costs for family doctor counseling (14.8%). The WTP for TIS was varied in the second approach. The influence of the productivity costs can be seen under the evaluation from the health care payer perspective. The cost of the family doctor is likely highly variable because of the modal distribution.

**Figure 9: Sensitivity of Incremental Net Benefit to Input Variables**



#### 4.3.2 Results of the Analysis under the Second Approach to TIS Benefits

As described above, the second greatest source of variance was the WTP for TIS. One of the major assumptions about WTP for TIS was that the user would have confidence in the skills of the IP. This was the second most important attribute in terms of the amount of utility gained by having the preferred level. However, it is possible that in some situations users will not have confidence in the skills of the IP at a TIS if it is an unknown program. The results of the analysis with reduced WTP for TIS are shown in Table 47.

**Table 47: Results of the Probabilistic Sensitivity Analysis for the Second Approach, Productivity Costs Included**

	Mean (\$)	SD (\$)	Median (\$)	Minimum (\$)	Maximum (\$)	Probability that value is greater than zero (%)
Incremental Benefits	10	12	10	-23	45	78.7
Incremental Costs	-20	-24	-19	-78	63	20.6
(Incremental Benefits)- (Incremental Costs)	30	27	29	-58	101	86.2

The results are still favourable towards TIS even when the user does not have confidence in the skills of the IP. The probability that the INB will be positive decreased from 99% to 86%. The mean INB of TIS compared to a family doctor visit decreased from \$63 to \$30.

### 4.3.3 Results of the Analysis from a Health Care System Perspective

#### 4.3.3.1 First Approach to Measurement of TIS Benefits

The results of the analysis using the first approach to TIS benefits when productivity costs were removed are shown in Table 48.

**Table 48: Results of Analysis from the Health Care System Perspective, First Approach**

	Mean (\$)	SD (\$)	Median (\$)	Minimum (\$)	Maximum (\$)	Probability that value is greater than zero (%)
Incremental Benefits	45	14	45	1	94	100.0
Incremental Costs	1	19	2	-43	51	55.5
(Incremental Benefits)- (Incremental Costs)	44	23	43	-22	111	97.0

In this analysis, the probability that the TIS costs exceed the costs of family doctor visit was %. The overall interpretation of the results is unchanged, as the INB of TIS compared to a family doctor visit is almost certain to be positive (%) and the mean INB is \$44.

### 4.3.3.2 Second Approach to Measurement of TIS Benefits

The analysis from the health care system perspective was run again with the reduced WTP for TIS. The results from this analysis are presented in Table 49.

**Table 49: Results of Sensitivity Analysis for Model Uncertainty from Health Care System Perspective**

	<b>Mean (\$)</b>	<b>SD (\$)</b>	<b>Median (\$)</b>	<b>Minimum (\$)</b>	<b>Maximum (\$)</b>	<b>Probability that value is greater than zero (%)</b>
Incremental Benefits	9	12	10	-34	45	77.7
Incremental Costs	2	18	3	-42	48	56.6
(Incremental Benefits)- (Incremental Costs)	8	22	7	-72	72	61.8

In this analysis the probability that incremental benefits exceeded incremental costs declined, but it was still likely to favour TIS most of the time (62%). The mean INB is \$8.

## 4.4 Discussion

### 4.4.1 Summary of Key Findings

This incremental comparison of net benefit found that TIS counseling results in a positive INB compared to family doctor counseling, suggesting an average savings of \$69 per consultation. These results were insensitive to changes in WTP for TIS. The positive INB was observed when the analysis was from the societal and from the health care system perspective. WTP for TIS was almost always higher than WTP for family doctor services, primarily as the scenarios were configured to assume that TIS provide very helpful information and that family doctors provide somewhat helpful information. The ability to provide information that was very helpful was the most important attribute and therefore had the highest attached WTP value. WTP for TIS was the second largest contributor to variance in the calculation of INB. WTP for a family doctor consultation was approximately two-thirds that of TIS (\$79 vs. \$124), and costs of service provision were approximately the same. Productivity costs for using a family doctor were three times those for TIS (\$46 vs. \$12).

## 4.4.2 Discussion of Methodological Challenges

While use of DCEs in health care settings has increased in recent years, to date no previous studies have used WTP results from a DCE within a CBA framework [330]. As noted by Drummond et al, “most of the published health care contingent valuation studies are experimental in nature, attempting to explore measurement feasibility issues rather than being full programme evaluations using CBA.” [97]. A few studies have used WTP values generated by contingent valuation in a CBA framework. A pharmacist led health promotion program was evaluated in a CBA where WTP and cost savings were added to obtain program benefits. WTP for the program was low but cost savings existed, therefore it was concluded that benefits of the program outweighed costs [186]. An evaluation of a new insulin formulation found that patients were willing to pay twice what the drug cost [331]. An evaluation of a new ovarian cancer drug with fewer side effects than others in its class found that WTP was less than the marginal increased cost for the drug, even though it was more preferred by patients [181].

Full program evaluations using WTP values generated by DCEs have not been identified in the literature. As discussed previously, there are still many limitations and methodological issues to be resolved around the appropriate design, format, and analysis of DCEs (see chapter three). It is also still unclear how best to use the WTP values generated by DCEs in a CBA framework. As this is the first full CBA of TIS and likely one of the first full CBAs using DCE data, most of the discussion section will examine methodological challenges of the study rather than provide comparisons of these findings with previous literature.

### 4.4.2.1 Estimating Willingness-to-Pay

One of the limitations of the WTP estimate is that it is restricted to the framing question used in the DCE [330]. Respondents were asked about how much they would be willing to pay for counseling when they have a question about the use of anti-depressants during pregnancy. Therefore the conclusions regarding the cost-benefit of TIS will only be applicable to this type of question. It is also possible that attributes and levels were not appropriately assigned, or that relevant attributes were not included in the DCE. It is unclear whether the stated preferences gathered through the DCE are truly representative of real life behaviour and choices.

Generalizability is a problem for many evaluation methods. For example, you can't assume that the QALYs gained from a hip replacement will be the same as for a knee replacement. The researcher should give consideration to this when designing a DCE or another WTP survey. TIS counsel women planning pregnancy, breast-feeding women and HCPs regarding a wide range of inquiries, and the cost-benefit of TIS determined in this study will not be generalizable to other caller groups or to different types of questions. The anti-depressant scenario was chosen as it is a very common inquiry at TIS and represents a situation in which there is some uncertainty about risks and benefits. The value of TIS to HCPs and the overall value of the knowledge translation activities of TIS were also not captured in this study. It is likely that providing information to one physician may be of more value as they can apply this information to numerous patients. Please refer to chapter three for a detailed discussion of the limitations of DCEs.

Assigning appropriate levels to the service scenarios provided some challenges. For example, the attribute "confidence in the IP" is difficult to attribute with certainty, therefore it was decided to assign the level of "have confidence" to both TIS and family doctor services in the primary PSA. WTP for TIS was found to be the second largest contributor to variance in the CBA. In the sensitivity analysis for measurement uncertainty, the overall conclusions were not altered when WTP for TIS was lowered after setting the level of confidence to "unaware of IP skills." This is likely because WTP for TIS was still higher than for family doctor services, but by a smaller margin. It was also assumed that TIS would provide information that was very helpful whereas the family doctor was assumed to provide information that is somewhat helpful. While this may often be the case, it may not always be so, both in terms of the reality of the quality of information provided and according to the patient's perspective (i.e. they believe their family doctor's information has been very helpful, even if they may not have received the highest quality of information), and is another case of model uncertainty that arises when WTP is defined in terms of the presence or absence of levels.

It was found that higher utility was achieved when the IP was known to the user. It is possible, therefore, that utility may increase for repeated users of TIS as they may come to know the IP over time. The changing WTP with repeated uses of either TIS or family doctor services was not captured in the CBA. The framework for this evaluation was defined as one consultation. If the framework were to be extended to include future or repeated consultations, including consultations on other topics, this would alter WTP.

In Toronto, Canada, where respondents were recruited, most people receive their primary health care services through a publicly funded system. Previous studies have found that some Canadian survey respondents have difficulty answering questions regarding WTP for health care services due to social values related to payment for these services and unfamiliarity with health care costs [245]. Other surveys have found it possible to elicit WTP from Canadian respondents [244-246]. The extent to which respondents were hindered by their social values and experiences of living in a public health care system is unknown. There appeared to be no “protest votes” in the DCE and focus group participants and pilot study participants did not report difficulty with assessing WTP. The sample was also urban-based, which may limit generalizability to other areas, and respondents were also generally of a high socio-economic status.

#### **4.4.2.2 Aggregation of Willingness-to-Pay for Attribute Levels into Total Willingness-to-Pay for a Service Encounter**

It was not expected that the total WTP for a service encounter would exceed \$90, the ceiling cost provided in the survey. Total WTP was higher than \$90 under the first scenario (mean \$124, 95% CI 93-164). This was concerning, as some respondents had never chosen a service that cost \$90, and the focus group participants mentioned \$100 as the maximum they would be willing to pay for a service encounter, so it was unclear whether this WTP estimate was robust. The previous DCEs of women’s health that had included WTP values were examined again (data originally shown in Table 12). It was found that in most previous studies, if all preferred attribute levels were present, total WTP generally exceeded the ceiling WTP cost cited in the survey.

**Table 50: Comparison of Aggregated Willingness-to-Pay Estimates to Ceiling Costs in Previous Discrete Choice Experiments**

Reference	Topic	Total WTP for preferred attribute levels (£)	Ceiling cost provided in survey (£)
Ryan 1997 [214]	Miscarriage management	848	600
Ryan 1999 [169]	In-vitro fertilization	3030 (highest income group)	3000
		1515 (lowest income group)	
San Miguel 2000 [215]	Menorrhagia treatment	8829 (highest income group)	5000
		5828 (lowest income group)	
Ryan 2005 [221]	Pre-natal diagnostic testing	791 (comprehensive karyotype analysis)	500
		690 (simple rapid diagnostic test)	
Seston 2007 [227]	Provision of emergency contraception	56*	50

\*Does not include WTP for decreasing waiting time and increasing opening hours of the service as these were provided in terms of WTP for one additional unit of time.

Taylor (2003) [219] and Wordsworth (2006) [225] were not included in this table as they provided WTP values in terms of changes in units (e.g. WTP for reducing wait time by one day) which does not permit meaningful aggregations of total WTP. This table reveals that aggregated WTP values may exceed the ceiling cost provided in the survey. This is a limitation of these studies. The validity of the aggregate WTP remains in question when it exceeds the ceiling level, since its determination is based on a linear extrapolation and it is unknown whether the linear relationship holds at values above those evaluated in the survey. The slope of the marginal utility of money remains unknown past the ceiling cost.

#### 4.4.2.3 Cost Estimates

One of the most uncertain values was the estimate of TIS costs. The only available information on TIS costs, the survey of North American TIS, had a small number of service budgets (13) and what cost items were included in these budgets varied. In fact, most of these data were not useful to estimating a cost per consultation. The budget and service data were skewed, as practices

between TIS vary widely. It was for these reasons that costs were estimated using external salary data. The cost per consultation is probably highly variable, and may be more variable than what was assigned in this analysis. The TIS cost components contributed little to the variance of the INB (see Figure 9), however this could be due to the fact that their distributions were more often normal and had smaller ranges compared to the triangular and modal distributions. As mentioned in chapter two, it is important for TIS to improve measurement of costs in order to better conduct future economic evaluations. If the cost per consultation at TIS was under-estimated, it is more likely that the INB will be reduced and it will be less likely to be positive.

The costing of TIS was conducted from the approach of determining the unit cost of one consultation. The cost per call in actual practice may be more desirable to decision-makers, which would also reflect to what extent the TIS is working at capacity. A TIS counselor probably has the capacity to answer two to three calls per hour, yet few TIS appeared to be operating at full capacity when calls per year was compared to counseling FTEs in the TIS survey. When TIS operate close to full capacity, the cost per consultation will be lowered due to increased efficiency. This analysis did not take into account issues regarding efficiency and capacity. Funding decision-makers may wish to know more about service utilization. For example, if there is a full time counselor dedicated to answering calls, yet they only receive one call per day and perform no other duties, this becomes a very expensive service. This issue raises the question of whether economic evaluations should compare alternative interventions to the status quo under perfect conditions, or under reality, where inefficiencies and waste are likely to occur. Perhaps the best use of these data will be for the benefits estimates to be compared with local costs, rather than trying to estimate a cost that could be applicable to all TIS.

The costs for family doctors may have been overestimated depending on how the anti-depressant exposure question is incorporated into a general consultation. If it is part of a general discussion about pregnancy, the doctor may not bill for it specifically. Billing practices in this area of medicine are unknown. If the cost of the consultation was overestimated, the probability that the INB was positive would decrease. Family doctor costs may also have been underestimated, as travel costs were not included. Inclusion of travel costs may have a more profound impact in rural settings. If travel costs had been included it may have resulted in a greater mean INB.

While overall costs were highly variable, this is a common problem in economic evaluations, particularly in health care settings. Every effort was made to estimate costs in a logical and transparent manner. Conducting the PSA also helped to understand how robust the INB estimates were despite uncertainty in the input data by determining the probability that the INB was positive rather than providing a single point estimate based on uncertain data.

#### 4.4.2.4 Other Methodological Challenges and Future Directions

A family doctor's office was used as the service comparator. This informed the selection of attributes and levels. Women with questions in pregnancy may try to acquire information in several other ways (e.g. the internet, pharmacist, or querying other HCPs). The preference for other information sources was not assessed. Additionally, it is unknown whether people will seek multiple sources of information after a counseling experience; for example, a woman may still ask her doctor after consulting a TIS and vice versa. Another approach entirely to this study could have been to study changes in health service use patterns. Indeed, it has been suggested that a cost-consequence framework be employed in economic evaluations of telemedicine [156].

It was assumed that patterns of health care use would not be different in the two services compared, and therefore other health care costs were not considered. This may have resulted in an underestimation of costs for the family doctor service. When counseling about pregnancy risk occurs without high quality information, HCPs may rely more heavily on diagnostic ultrasound or other costly interventions, which could be an important cost difference that was not considered in this evaluation. A survey of users of a TIS based in Utah found that following counseling by TIS, respondents rated themselves as significantly less likely to visit their doctor and to request a diagnostic ultrasound [143]. It was estimated that counseling by this TIS might prevent 189 diagnostic ultrasounds and 357 prenatal care provider visits per 3,000 callers [143]. A previous evaluation of a telephone counseling intervention for patients with serious and persistent mental illness found that patients who received telephonic counseling were less likely to visit the emergency department [332]. Other studies have also found that telephone services can avoid emergency department and physician visits [150-152]. It is possible that the cost savings of telephone-based interventions are better examined by studying changing patterns of health care use. In relation to anti-depressant use during pregnancy, it has been found that women who receive inadequate assistance with medication decision-making and stop using their

medication abruptly may be hospitalized, experience suicidal ideation, and increase use of harmful drugs such as alcohol [30]. A future study of patterns of health care use amongst TIS users and non-users would help to address the question of whether costs may have been underestimated for family doctor services.

## 4.5 Conclusions

Many challenges exist in conducting an economic evaluation of a telemedicine intervention. It is difficult to identify and quantify the benefits obtained from an information-based intervention. Further challenges exist when evaluating any intervention in the context of pregnancy, as two individuals must be simultaneously considered. Specific challenges include the inappropriateness of evaluating individual utilities in traditional economic evaluation techniques when measuring health outcomes for a mother-child dyad, and the valuation of non-health outcomes such as reassurance [156]. To address these issues, a CBA was conducted using WTP values generated by a DCE. While using WTP to measure program benefits goes some way towards a valid valuation of benefits, and also allows the measurement of non-health outcomes, this technique comes with its own host of methodological limitations. Gold standard methods for the use of DCEs and their results in a CBA framework have not yet been established.

This CBA found that the INB for a single TIS consultation on anti-depressant use during pregnancy was almost certain to be positive (probability was 99%), and the mean INB per consultation was \$63 (SD 28) under the first approach and \$30 (SD 27) under the second approach. While these findings are limited by uncertainty regarding cost and benefit estimates, they suggest that TIS provide a positive net benefit primarily due to their ability to offer specialized high quality information and reduce productivity losses. This finding is in accordance with other previous research that has found reports of high satisfaction with TIS amongst both members of the public and health care professionals [77, 85, 87].

## 5 Chapter 5: General Discussion of Findings

### 5.1 Discussion of Main Findings

It was hypothesized that a TIS encounter would provide a positive net benefit compared to a standard physician encounter for counseling about anti-depressant use during pregnancy. The cost-benefit analysis found that TIS benefits were higher than those for physician counseling, and that overall costs were lower. Service costs for both interventions were approximately the same, but TIS productivity costs were lower. The probability that TIS provides a positive incremental net benefit was 99% from the societal perspective (productivity costs included for a single encounter). This finding is in agreement with previous research that has found that satisfaction with TIS is high, counseling may decrease use of other health care services, and appropriate counseling improves health outcomes [85, 87, 143, 189].

There were three specific objectives of this thesis work: 1. To determine the structure, functions, and operating costs of North American TIS; 2. To determine public preferences and WTP for TIS and physician care attributes using a discrete choice experiment; and 3. To compare WTP for TIS and physician care to their respective program costs in a CBA for a single encounter regarding anti-depressant use during pregnancy.

With respect to the first objective, it was found that most TIS are small, with approximately two full time employees. It appeared that staff salaries account for the largest portion of service costs. While practices vary among TIS, they are mainly responding to inquiries from pregnant women, breast-feeding women, and their HCPs, and the inquiries are most often regarding exposures to medications. Approximately half of TIS in North America regularly participate in research, whereas amongst European and other international sites this proportion was much higher. TIS are most commonly found in university-affiliated hospitals, but in a variety of departments. The descriptions of TIS activities were limited by their retrospective, self-report format; particularly, only about two-thirds of TIS were able to provide accurate information about program budgets. The structure and size of TIS varied widely between services, as did numbers of calls per week. The field of teratology is relatively new, and issues unique to this medical area will be discussed in section 5.1.1.

The DCE found that the most important feature of teratology counseling was the provision of information that is very helpful. The method by which the information was provided was less important; however there were some subgroups for whom features such as training of the IP were important. Having some sort of relationship with the IP was also of importance, as both knowing the IP and having confidence in their skills were preferred attribute levels. Of interest was the finding that survey respondents with lower education levels valued the provision of very helpful information less than respondents with higher education levels. Also, the level of anxiety the respondent felt about the exposed pregnancy was closely related to their WTP. Income did not affect preferences or WTP, perhaps because this was a one-time expenditure or because price levels were not set high enough.

While DCEs are an increasingly utilized research tool, methodological questions persist. The data will always be confined by the attributes and levels selected for evaluation. This DCE was also limited by framing the question in the context of a pregnant woman exposed to an anti-depressant. It was, however, thought to be more appropriate than a CEA or CUA, which would have measured benefits in terms of health outcomes rather than dollars. The use of WTP values derived from a DCE in a CBA has not been well explored, and to our knowledge this may have been the first full program evaluation using such data. Several methodological challenges were encountered and will be further described in section 5.1.3.

The finding that members of the public valued the content and quality of health information more highly than the vehicle by which it is provided may be important in the future as health care systems evolve away from the traditional model of family doctor as health care gate-keeper, and grow to incorporate other potential modes of health information delivery. These may include non-physician care providers, telehealth lines, internet sites, and even text messages [333, 334]. Health care preferences will be discussed in section 5.1.4. Overall conclusions and future directions will then be provided.

### 5.1.1 Teratology Counseling and Drug Safety Surveillance

Medications are currently released onto the market with very little, if any, study of their effects on human pregnancies. In fact, pregnant women are actively excluded from most clinical trials. Data on pregnancy exposures, therefore, are mainly gathered through drug safety surveillance. One of the reasons the need for TIS is so great is because safety data are often limited and may

be difficult to interpret. An obvious solution to this problem is to improve the quality and quantity of data regarding exposures during pregnancy so that decision-making is better informed. This can be achieved through better drug safety surveillance, more research in the areas of maternal and reproductive health, and increased use of pregnancy registries [205, 335]. Changes to the safety labeling of medications are currently underway, which may help to decrease confusion and anxiety, and to better aid physicians in providing advice [81].

In 2002, the FDA released guidelines for the pharmaceutical industry on how to establish registries and monitor outcomes [336]. Yet in the intervening seven years, many opportunities to study pregnancy exposures have been lost. The quality of data within existing pregnancy registries could be improved by more specifically tracking the timing and dose of exposures, a change which has been called for by the OTIS research committee [337]. Perhaps there is a way for TIS to partner with pregnancy registries to better track exposure data. An attempt to link TIS data with wider registries improved the amount of pregnancy follow-up information available in one project [338]. The risk for TIS is that by collaborating with drug manufacturers, their findings may appear biased. Another way to improve pregnancy exposure data is for pharmaceutical companies to better study and develop drugs intended for maternal use, however, currently there is no financial incentive for them to do so as the market for such products is small [74]. There is a clear need for an improvement in post-marketing surveillance of medication use during pregnancy, which will lead to better data to inform counseling and decision-making.

## 5.1.2 Methodological Issues

### 5.1.2.1 Economic Evaluations

Economic evaluations of health care programs are increasingly used to inform health care decision-making. Recent years have seen the development of agencies such as NICE (National Institute for Health and Clinical Excellence) in the UK, IQWiG (Institute for Quality and Efficiency in Health Care) in Germany, and the CDR (Common Drug Review) in Canada, whose mandates are to rigorously evaluate health care interventions for both effectiveness and cost-effectiveness, and provide recommendations and guidelines to their country's respective health care programs regarding funding of these interventions. Correspondingly, appropriate methodological guidelines for conducting economic evaluations must be developed to ensure

that data are of a high quality and are useful to decision-makers [28]. The very idea of measuring health is complex, and not surprisingly the appropriate way to measure it is debated.

NICE commonly measures health outcomes in QALYs (Quality Adjusted Life Years). A QALY is a combined measure of quantity and quality of life, determined by adjusting the length of time in a given health state by a utility (on a scale of zero to one) for that health state [97]. The incremental cost per QALY gained is determined and if an intervention falls above a certain cost per QALY threshold then the intervention is generally rejected. As NICE is a leading agency in this field, most others have followed suit in using the QALY as the measure of health benefit. However, there are problems with QALYs, as was discussed in chapter three. One problem is where to set the threshold over which an intervention is deemed too costly – what is society willing to pay to gain a QALY [339, 340]? Another issue is consideration of opportunity costs: what programs will be forgone in order to fund one that provides QALY gains under the threshold [341]? A critique common to any economic evaluation is that complex issues and decisions are oversimplified [342]. In light of these criticisms, evaluations using the cost-benefit format and WTP as the measure of benefit have recently become more attractive. Again, however, appropriate methodologies need to be developed (see section 5.1.3.2). The ideal methodology by which to evaluate the economic value of health interventions will continue to be debated. At this stage it is difficult to choose a method of measuring health benefits that is without limitations.

Pregnancy is a unique time period that offers many opportunities to lay a foundation for long-term health. However, as two patients must be considered simultaneously in any evaluation of effectiveness, and as pregnancy complications are multi-factorial, evaluations of prenatal care are challenging. Outcomes such as spontaneous abortion are extremely difficult to quantify. Child health outcomes may occur temporally distant from the intervention (e.g. school performance). A further complication of full evaluations of prenatal care is the variety of stakeholders affected by improved child health, including the education and justice systems [104]. An issue specific to performing evaluations in the context of pregnancy is the aggregation of health outcomes for the mother and the baby. An evaluation of an intervention to reduce mother-to-child transmission of HIV and HCV added the QALYs for each person together [343]. There is currently no accepted method for combining QALYs for two people. There is also

debate over when to start counting the QALYs of a fetus [160, 344]. As interventions in the prenatal period improve, this issue will increase in importance.

The lack of evaluation in this field makes it difficult to inform payer decision-making [101, 104]. A few economic evaluations of prenatal care have been performed, regarding timing and volume of prenatal care interventions and treatment of maternal diabetes, and these have found a positive return on investment [104, 345, 346]. The difficulties in adequately measuring the effectiveness of prenatal care can be nicely summarized in a quote attributed to Albert Einstein: “not everything that counts can be counted; not everything that can be counted counts.”

### 5.1.2.2 Willingness-to-Pay and Discrete Choice Experiments

As discussed in chapter three, many of the methodological choices that need to be made when designing conjoint analysis studies lack clear guidelines. For example, how many choice tasks to ask, attributes to include, and options to provide is debated and will likely differ between studies. Appropriate ways to account for uncertainty in DCE data are also unclear, as statistics such as confidence intervals may be calculated differently and there is no current gold standard [295]. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has a special interest group currently formulating guidelines for the appropriate design, administration, and analysis of conjoint analysis studies, which may help to address the wide variations in current practices [347].

Appropriate definition of the cost attributes and levels is an area that deserves further consideration. In this DCE, the valuation of the cost attribute was not found to be linear, that is, even though each level increased by \$40 (\$10, \$50, \$90) the amount of disutility from moving from the \$10 to the \$50 level was not the same as moving from the \$50 to \$90 level. However, the marginal utility of money calculated from the slope of these data points assumes linearity. The correct adjustments to be made when the data points are not linear are not currently known. In our study, we conducted a sensitivity analysis where only the slope between the \$50 and \$90 point was used, which will have to be linear as it is only between two points. Using this slope may be an overestimation of the marginal utility of money [314]. We also calculated CIs through bootstrapping. Including another cost level (e.g. \$130) would have provided one more data point, which may have helped determine an accurate estimation of the slope representing the marginal

utility of money. Increased experience with this method may help to provide better guidance in determining the appropriate cost levels, which will improve WTP estimates.

There are still outstanding methodological issues to be resolved regarding WTP values derived from DCEs. First, determining if people will pay in real life what they say they will in WTP studies is difficult. In most developed nations, basic health services are provided free at the point of service through a publicly funded system, which makes establishing actual WTP particularly difficult for health care services. Empirical evaluations of the external validity of WTP values have so far been favourable [324]. Internal validity of DCEs is also generally considered to be good [167, 168, 313]. An advantage of WTP over other benefit measures such as the QALY is that on an individual level, respondents may take into account opportunity costs to themselves, as they are asked how much they would give up of a finite pot of their own resources to obtain a benefit, which presumably means going without something else [341].

It should be mentioned that the goal of measuring WTP for teratology counseling was not to set user fees. Some TIS have previously employed user fees to mixed degrees of success.

Anecdotally, one TIS reported a decrease in call volume of about 64% following the institution of user fees. The user fee for the public was nominal, whereas institutions and private doctors were charged annual subscription fees. Conversely, another TIS reported that professional subscriptions to their service were able to cover one third of their operating expenses, with no negative impact on call volume [348].

### 5.1.2.3 Using Willingness-to-Pay Values in a Cost-Benefit Analysis

A DCE provides utilities attached to the levels of the attributes of interest. To obtain a total WTP value, the individual utilities for each level are summed to create a scenario profile. In this study, assigning levels to the scenarios was problematic. For example, “confidence in the skills of the IP” was an important level, yet is difficult to assign to a hypothetical service with certainty. This may lead researchers to conclude that it is best to use DCEs for program evaluations when the levels can be assigned with certainty. An example of this would be determining which colorectal cancer screening method is preferable by determining how much patients prefer to provide stool rather than receive an endoscopy [270]. However, one of the main advantages of DCEs is that they are better able to value process utility than other methods of evaluation. For example, the value of meeting with health care staff that have positive attitudes can be estimated [169, 349].

Yet this is the kind of attribute level that is difficult to assign to a service scenario with certainty. A researcher may be in a position of finding out how much value is gained when a person speaks with a HCP with a positive attitude, yet is unable to then extrapolate that finding to definitively state that service A is preferred over service B, because staff attitudes can vary from day to day. In our CBA, we performed a secondary PSA where the service scenarios were altered. This is one possible solution when one is in a position of having attributes that are difficult to definitively assign to service A or service B. There may be other methods for addressing the design of service scenarios when it is planned to aggregate utilities or WTP values for a program evaluation, and further consideration of these issues would be welcomed.

At this point, DCEs may best be used in a program design stage, to improve service delivery, or to understand patient decision-making. Using DCE WTP data in a full CBA is a novel approach and therefore may not be widely accepted. However, many previous researchers have commented on the potential for DCEs to be used in program evaluations [313, 330, 349]. Some of the issues identified through this work should be addressed in order to support further use of this method. It can be argued that in many ways, a CBA using WTP values derived from DCEs is more firmly rooted in societal values, and therefore welfare economics, than a CEA. A CEA determines the cost of obtaining an improvement in a single health outcome. Health care decision-makers determine if that cost is acceptable given program budgets. WTP values generated from surveys of patients and/or community members are a reflection of societal WTP for a given intervention. Moreover, community respondents may consider benefits to others in their choices. But to feel confident in using these WTP values, we must first feel confident that people are responding honestly and thoughtfully to the surveys, and that the surveys are appropriately designed. A greater focus on patient and community values may serve, in the long term, to increase the quality of health care systems, as they become more reflective of public preferences.

#### 5.1.2.4 Methodological Issues Related to Evaluating a Telehealth Intervention

Telemedicine and telehealth interventions may be particularly difficult to evaluate using the current economic evaluation frameworks (CEA, CUA, and CBA). As stated by McIntosh and Cairns, “In telemedicine, the evaluation will often be of the vehicle or mode of provision, rather than the provision itself. Hence, in many evaluations, it will be difficult to attribute health

benefits...to telemedicine itself. That is, even if changes in health outcome are due to telemedicine it will be difficult to quantify this.” [156] McIntosh and Cairns go on to advocate a cost-consequence framework, whereby the cost of an intervention is classified as either cost saving, little difference in cost, greater costs, or insufficient evidence, and similarly the consequences of the intervention are divided into four classes: beneficial, little difference, negative, or insufficient evidence. An intervention can then be classified into one of 16 cells. For example, little difference in cost and beneficial consequences would indicate that a service was worthwhile [156]. This general framework has not been widely applied, but it is important to acknowledge that telehealth interventions are different from other health care interventions and therefore may require unique evaluation approaches.

Changing patterns of health care use are another way in which telehealth interventions are unique, and may in fact be a better way to capture costs and consequences. A Utah TIS demonstrated through a survey that their counseling recipients were less likely to visit their doctor and less likely to request a diagnostic ultrasound after being counseled by the TIS [143]. These findings should be verified through real health resource use data, and such a study is recommended as a future direction (see Section 5.2.2).

### 5.1.3 Health Care Preferences

It is increasingly recognized that taking patient preferences into account is important to improving the effectiveness of health care programs [213]. This DCE demonstrated that people care less about how health information is delivered, so long as it is of high quality and comes from a trusted source. An evaluation of a Quebec-based general telehealth line reported that the most beneficial aspects of the program, according to its users, were speed of access, obtaining more health information, and avoiding travel costs [150]. These attributes are similar to the preferred attributes in this DCE. In this DCE, previous Motherisk users attached less value to speaking with a known HCP, which indicates that people may become more comfortable with receiving health care information in novel ways as they experience them.

The health care system lags behind in using new technologies to communicate with patients. Health care systems should embrace new information technologies that allow for rapid communication with patients in modes that are convenient to the patient. This would include not just telephone communication, but also websites, and even instant messaging and social

networking sites. Such programs will of course need to be rigorously monitored for quality, but it is important to note that as society continues to embrace mobile and smart phones and computer and internet access becomes more widespread, there are opportunities to improve the availability of health information.

One of the more interesting elements of the DCE was identifying subgroups with varying preferences. The provision of information that was very helpful was the most important attribute, yet people with higher education levels (at least college or university degree) placed higher value on receiving very helpful information than people without a college or university degree. This finding highlights the importance of understanding social determinants of health. It has long been known that health disparities exist between wealthy and poorer people, even in countries that provide social assistance and free basic health care coverage such as Canada [305]. This finding is an example of why it is important to measure preferences, as it may help to understand why some programs are successful and others are not. There are some subgroups and cultural groups who still rely heavily on the guidance of their HCP, whereas others may prefer to have autonomy over their decisions and decide themselves after gathering information. It is important to be aware of varying preferences. Understanding preferences may help to improve program uptake.

#### 5.1.4 Applying the Health Belief Model to TIS

Health programs are taken up by society to varying degrees of success. TIS are an example of a program that has thrived in some settings, and struggled for clients in others. Social psychologists have developed the Health Belief Model (HBM) to explain people's decisions to take part in health programs [350]. The six constructs of the HBM used to explain the decision making process around health program participation are that individuals:

1. Believe they are susceptible to the condition (*perceived susceptibility*)
2. Believe the condition has serious consequences (*perceived severity*)
3. Believe taking action would reduce their susceptibility to the condition or its severity (*perceived benefits*)
4. Believe costs of taking action (*perceived barriers*) are outweighed by the benefits

5. Are exposed to factors that prompt action (e.g., a television ad or a reminder from one's physician to get a mammogram) (*cue to action*)
6. Are confident in their ability to successfully perform an action (*self-efficacy*)

Understanding these constructs and applying them to health programs can help to better understand a program's success. A conceptual framework incorporating the HBM may be a future direction to better understand the success of TIS and to identify areas for improvement.

A cursory application of the HBM to teratology counseling by TIS reveals that potential barriers to service uptake exist via constructs three, five, and six. For construct three (perceived benefits), gathering information *after* an exposure has already occurred may not have an impact on the condition or its severity. For example, for some women there may be no action for them to take if they learn that their exposure may have harmed the pregnancy, as they may personally not consider termination of pregnancy an option. Or, specific prenatal diagnostics may not be available (e.g. for brain damage), or the public is unaware of what diagnostic or interventional tools are available. For construct five, cues to action may not exist as TIS do not generally advertise. For construct six (self-efficacy), similarly to construct three, there may be few options to mitigate the effects of a one-time pregnancy exposure that has already taken place. In order to maximize use of their services, TIS may need to better explain to the public how information can be of use even after an exposure has occurred. Information in itself has value. The public also may not be aware of advances in fetal diagnostics, treatments, and surgeries that can successfully correct birth defects and treat fetal conditions. Increased awareness of TIS overall is also important to improve cues to action.

### 5.1.5 The Role of Risk Perception and Communication in TIS Utilization

Teratology counseling is, in essence, risk communication. Risk perception and communication has received considerable attention in the areas of public and environmental health. TIS are a public health service that most often engages on an individual level rather than a population level. Still, some of the principles of risk perception and communication are important to consider in an examination of TIS. Risk communication research has found that similarly to the HBM, the desire for risk information is related to the extent to which individuals believe they have control over an issue [351]. Individuals generally act based on their perception of risk

[352], and indeed a relationship was found in the DCE between anxiety and WTP. Risk communication can be complex. It may require a grasp of statistics and probabilities, and often people tend to overestimate risk to themselves, particularly in the field of teratology [353, 354]. Other factors affecting risk perception include the trustworthiness of the information source and the relevance of the risk to everyday life [355]. It has been found that risk communication is more successful when the message is tailored to an individual rather than provided at a population level, and is more effective in changing outcomes when patients are making choices about treatment rather than participating in screening or changing risky behaviours [356].

In relation to TIS, it can be seen that risk perception is high which should be a strong motivator to action. It is important that TIS be seen as a trustworthy source of information. It is also important that it be understood that TIS can help to provide individualized assessments of risk. TIS ask about the dose and timing of an exposure as well as other pregnancy risk factors prior to providing risk assessments to individual callers. Perhaps there is low awareness of the fact that TIS can provide individualized risk assessments. Again, it is important to understand that if people feel they have no control or options the risk information may not be of use to them.

### 5.1.6 Generalizability of Findings

The WTP estimates were generated with respect to an exposure to an anti-depressant during pregnancy. WTP for this type of exposure may be different than for other exposures, for example, exposures that are perceived to be potentially less harmful may correspondingly have a reduced WTP. This was seen in the DCE, as there was an interaction between respondent's stated anxiety level and their WTP. The scenario in the DCE also specified that the exposure had occurred in the first trimester, which is the period of risk for malformations; while complications may occur in the second and third trimesters, these periods may be seen as less risky, and therefore WTP for exposures that occur outside of the first trimester may also be less. Many inquiries to TIS are regarding exposures during lactation; in North America, breast-feeding women were a mean of 7.5% of callers. WTP for exposures during lactation may be different than for those during pregnancy. The WTP of HCPs may also be different than the WTP of the public. HCPs represented 33% of calls to North American TIS on average. In summary, the WTP estimate is limited to a specific type of exposure during a specific time period, from the perspective of a member of the public. WTP estimates may vary for other types of calls. Varying

WTP estimates will vary the estimation of net social benefit. Another generalizability issue is related to the location in which the study was conducted. As previously mentioned, the study sample was Canadian, primarily female, urban, and well-educated. It was found that some demographic characteristics affect preferences; WTP was not affected by demographic characteristics in this study. WTP estimates may also vary in the U.S. where more health care costs are covered out-of-pocket and by private insurance companies. The findings of this study may not be generalizable to other types of teratology inquiries. Differences may exist between attitudes towards mental health issues and medications and other types of exposures. The WTP findings may be generalizable to other social groups but WTP may vary depending on people's experiences with their local health care system. The finding that anxiety affected WTP in an almost linear fashion may be useful to estimating WTP for other types of inquiries.

### 5.1.7 Limitations

Limitations have been outlined in other sections of this chapter and chapters 2-4. In brief, cost estimates for TIS were limited by a lack of real-world data and needed to be estimated based on multiple inputs. Costs are also likely to vary from setting to setting depending on TIS structure and operations, which are known to vary widely. The billing practices of doctors advising pregnant women on the use of anti-depressants are unknown, therefore the cost attributed to the family doctor consultation was highly variable. The estimation of WTP through a DCE is still a relatively new method in health economics, and requires further research to establish gold standard practices for survey design and analysis. WTP estimates here were limited to the attributes and levels evaluated in the survey, and may have been over-estimated as a none or opt-out option was not provided. DCE respondents were not representative of the GTA population, and may have been affected in their ability to estimate WTP by their experiences in a health system where care is free at the point of service. Common practices in CEAs (i.e. PSA, data presented in a cost-effectiveness plane) were adapted for the CBA. This has not been widely practiced before, therefore further research into appropriate methodologies may be required.

## 5.2 Conclusions

Many elements of this thesis work were novel. An economic evaluation of TIS has not previously been conducted, and this was the first detailed estimation of TIS costs per telephone consultation. There have been few DCEs that have evaluated preferences for health information

delivery, and fewer still that have examined preferences in the context of pregnancy risk information. CBAs are not often used in a rigorous manner, and this incremental CBA and the use of the cost-effectiveness plane to express CBA results were also novel approaches. Presenting the CBA data in a manner similar to how traditional CEA results are presented may facilitate interpretation and lead to increased use of this methodology.

Many methodological challenges to appropriately and validly measuring WTP for health care services still exist. In light of these challenges and current limitations, the finding that TIS counseling provides a positive net benefit should be considered supportive of continued funding of current TIS, however this conclusion is restricted to a specific type of inquiry and to one encounter, therefore further study is required. These findings are limited to the framing of the question used in the DCE, which was of a pregnant woman exposed to an anti-depressant; WTP for other types of inquiries will vary. The data supported the hypothesis that TIS offer increased benefits at a reduced cost, compared to physician services for counseling on anti-depressant use in pregnancy. Currently there are few alternatives for accessing the type of high quality information that TIS can provide. Policy recommendations and potential future directions are discussed below.

## 5.2.1 Implications for Stakeholders

### 5.2.1.1 Implications for Teratology Information Services

In light of the finding that the provision of very helpful information is the most important feature of a teratology counseling encounter, TIS should emphasize their specialized nature and their ability to provide high quality information in any marketing endeavour. It was also important to users to have confidence in the skills of the IP. Some TIS may need to improve their profile in their local communities to ensure that they are considered to be a reliable and trustworthy source of information. This may be achieved by increased networking with local obstetricians and primary care providers, whose support and recommendation of the TIS to their pregnant patients would inspire confidence. In the survey of TIS, a mean of 44% of referrals came from physicians, and less than 5% of referrals came from pharmacists. This indicates that there are opportunities for TIS to improve their networking with local health care providers.

As people may be unfamiliar with TIS, attaching themselves to a high profile institution, such as a university-affiliated research hospital, may also help to inspire confidence in the service, as the reputation of the facility will reflect onto them. It was mentioned by many participants in the focus group discussions with Motherisk users that they felt confident using the service because it was located in The Hospital for Sick Children, which has a very positive reputation in the Toronto area. Another option for TIS to consider is whether or not their counselors should be accredited, either through a unique designation, or some other form of standardized education and quality monitoring practices. Many allied health professionals have been integrated into the health care system, including midwives, nutritionists, respiratory therapists, occupational therapists, speech-language pathologists, etc. Whether such a designation is worthwhile or inspires confidence in the target populations is unclear. It is also unclear if TIS is too small a field to warrant an accreditation system at this point. Regardless, TIS should work to make it known that they are able to provide the highest quality of information regarding pregnancy exposures, and work to enhance their reputation as a trusted source of information.

Another important implication of this study for TIS is the increased awareness of the need to appropriately track TIS costs. Not all TIS were able to provide a budget and deriving a per-hour or per-consultation cost was difficult. This information is vital to any economic evaluation. Therefore TIS should increase efforts to track their costs so that more reliable budget data is available for future evaluations.

### 5.2.1.2 Implications for Health Care Decision-Makers

Health care decision-makers belong to various groups. Decision-makers interested in this topic in government may include the Canadian provincial Ministries of Health, and the U.S. Maternal and Child Health Bureau in the Dept. of Health and Human Services. Private organizations in the U.S. such as HMOs, and not-for-profit organizations such as the March of Dimes may also be interested in the findings of this work. Of interest to health care decision-makers was the finding that a specially-trained counselor was preferred over a family doctor with general health training. This finding may be applicable to other areas of health care as well. As long as such counselors are appropriately trained and monitored, they may be able to help ease the demand for primary care practitioners which many western nations are currently facing.

Also of interest was the finding that a telephone consultation was preferred over an in-person appointment. Many jurisdictions, including Ontario, have instituted a “hotline”-style health information program. Telehealth Ontario is staffed by registered nurses 24 hours a day, seven days a week, and is funded by the Ontario Ministry of Health and Long Term Care. The nurse’s role is to perform a basic assessment and to then provide advice as to whether the correct course of action is to perform self care, visit a health practitioner or contact emergency services [357]. They may also direct people to other appropriate community resources, with the goal of alleviating congestion at family doctor’s offices and emergency rooms [357]. A rigorous evaluation of the impact of the program on primary health service use has not yet been conducted, although it has been suggested that identifying types of calls may be useful for early detection of respiratory or other infectious outbreaks [358, 359]. It appears that crucial elements of imparting health information are not necessarily lost when an encounter occurs over the phone rather than face-to-face.

With respect to the specific findings about the cost-benefit of TIS, health care decision-makers should note that WTP for TIS is almost certain to be greater than the costs, under the assumptions made in our model, and for the anti-depressant counseling scenario described. Currently, most TIS in North America are funded by a combination of government funds and funds from the hospital in which they are located. Unstable funding has been a problem for many TIS. It is not possible to conclude from this project who is the appropriate funder of TIS. However, health care decision-makers should note that the results of this study indicate that the public places a high value on receiving the type of high quality information that most TIS provide.

### 5.2.1.3 Implications for Health Economics Researchers

This thesis used WTP values derived from a DCE in a full CBA. The internal and external validity of WTP values requires further research. Assigning levels to service scenarios when there is uncertainty (for example, regarding attitudes or feelings) is another area that merits further consideration. Appropriate calculation of confidence intervals around the WTP estimate, and how to estimate WTP when the marginal utility of money is not linear, are also methodological challenges. While some of these methodological challenges may make CBAs conducted with WTP values seem unattractive, there are many positive features of these types of

studies that support their merit and continued use: they are rooted in community values, and they provide better estimations of process utility and opportunity costs than traditional CEAs and CUAs.

If a health economics researcher wishes to undertake this type of study, it is recommended that they ensure the results will be useful to local decision-makers. Some agencies prefer CUAs above other types of evaluation and therefore may not accept such a report. Other decision-makers may be more comfortable with a dollars-to-dollars analysis, as this more closely resembles the data used to inform decisions in other settings. Up-front consideration should also be given to how the service scenarios will be configured. As well, the definition of what the “benefit” is that is being valued in the WTP survey should serve to inform how the costs should be measured (for example, the benefit in this study was for one consultation, therefore costs were also estimated for one consultation). The field of conjoint analysis is advancing, and subsequently full CBAs using DCE data are likely to become more common. This type of evaluation can be recommended when it is important to value multiple health outcomes and/or process utility is being estimated. Some methodological challenges, however, will continue to be faced until further research is conducted.

### 5.2.2 Future Directions

In the future, it is recommended that an evaluation of how use of TIS changes the consumption of other health care resources be conducted. This may be done retrospectively by recruiting a cohort of new mothers, determining if they have used a TIS, and then tracking their health service encounters through their pregnancy. This could also be done prospectively, where TIS callers are compared to women from a region where there is no TIS access. Such a study would need to take into account potential demographic differences between TIS users and non-users.

As previously mentioned, it would be easier for all HCPs, including TIS counselors, to provide counseling if there were larger and better drug exposure studies available. This may be achieved by increasing TIS participation in research. Many TIS in North America still do not participate in research. Increased use of existing pregnancy registries would also be beneficial.

There are many methodological issues surrounding the DCE method that still need to be resolved, particularly determining external validity, appropriate methods for the aggregation of

utilities, and addressing uncertainty. It may be time, however, for agencies such as NICE, IQWiQ, and the CDR to investigate incorporating preference-based evaluations such as DCEs into their decision-making processes.

## References

- [1] Petrini J, Damus K, Russell R, Poschman K, Davidoff MJ, Mattison D. Contribution of birth defects to infant mortality in the United States. *Teratology*. 2002;66 Suppl 1:S3-6.
- [2] Petrini J. Birth Defects and Infant Mortality: A National and Regional Profile: March of Dimes Birth Defects Foundation 1996.
- [3] Webster WS, Freeman JAD. Is this drug safe in pregnancy? *Reproductive Toxicology*. 2001;15:619-29.
- [4] Clementi M, Di Gianantonio E, Ornoy A. Teratology Information Services in Europe and Their Contribution to the Prevention of Birth Defects. *Community Genetics*. 2002;5(1):8-12.
- [5] Bonati M, Bortolus R, Marchetti F, Romero M, Tognoni G. Drug use in pregnancy: an overview of epidemiological (drug utilization) studies. *European journal of clinical pharmacology*. 1990;38(4):325-8.
- [6] Leen-Mitchell M, Martinez L, Gallegos S, Robertson J, Carey JC. Mini-Review: History of Organized Teratology Information Services in North America. *Teratology*. 2000;61:314-7.
- [7] De Santis M, Cesari E, Cavaliere A, Ligato MS, Nobili E, Visconti D, et al. Paternal exposure and counselling: experience of a Teratology Information Service. *Reproductive toxicology (Elmsford, NY)*. 2008 Sep;26(1):42-6.
- [8] Koren G. Maternal-fetal toxicology: A clinician's guide. 2 ed: Marcel Dekker 1994.
- [9] O'Brien J, Conover B, Frias J, Koren G, Quinn D, Robert E, et al. Formation of the Organization of Teratology Information Services (OTIS). The OTIS Executive Committee. *Reproductive Toxicology*. 1991;5(5):463.
- [10] Organization of Teratology Information Specialists. [cited 2009 January 28]; Available from: [www.otispregnancy.org](http://www.otispregnancy.org)
- [11] Scialli AR, Lione A, Padgett GKB. Reproductive effects of chemical, physical, and biologic agents, REPROTOX. Baltimore: Johns Hopkins University Press 1995.
- [12] Friedman JM, Polifka JE. Teratogenic effects of drugs: a resource for clinicians (TERIS). 2nd ed. Baltimore: Johns Hopkins University Press 2000.
- [13] Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet*. 1992 Feb 29;339(8792):530-3.
- [14] Pastuszak AL, Levy M, Schick B, Zuber C, Feldkamp M, Gladstone J, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *The New England journal of medicine*. 1994 Mar 31;330(13):901-5.
- [15] Feldkamp ML, Jones KL, Ornoy A, Pastuszak A, Rosenwasser S, Schick B, et al. Post-marketing Surveillance for Angiotensin-Converting Enzyme Inhibitor Use During the First Trimester of Pregnancy - United States, Canada, and Israel. *MMWR*. 1997;46(11):240-2.

- [16] Bailey B, Addis A, Lee A, Sanghvi K, Mastroiacovo P, Mazzone T, et al. Cisapride use during human pregnancy: a prospective, controlled multicenter study. *Digestive diseases and sciences*. 1997 Sep;42(9):1848-52.
- [17] Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrobial agents and chemotherapy*. 1998 Jun;42(6):1336-9.
- [18] Einarson A, Phillips E, Mawji F, D'Alimonte D, Schick B, Addis A, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *American journal of perinatology*. 1998;15(9):523-5.
- [19] Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *The American journal of psychiatry*. 2001 Oct;158(10):1728-30.
- [20] Chambers CD, Johnson DL, Macaraeg GR, Jones KL. Pregnancy Outcome Following Early Gestational Exposure to Leflunomide: The OTIS Rheumatoid Arthritis in Pregnancy Study (104). *Pharmacoepidemiology and Drug Safety*. 2004;13:S1-S334.
- [21] Felix RJ, Jones KL, Johnson KA, McCloskey CA, Chambers CD. Postmarketing Surveillance for Drug Safety in Pregnancy: The Organization of Teratology Information Services Project. *Birth Defects Research (Part A)*. 2004;70:944-7.
- [22] Robertson J, Polifka JE, Avner M, Chambers C, Delevan D, Koren G, et al. A Survey of Pregnant Women Using Isotretinoin. *Birth Defects Research (Part A)* 2005;73:881-7.
- [23] Djulus J, Koren G, Einarson TR, Wilton L, Shakir S, Diav-Citrin O, et al. Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes. *The Journal of clinical psychiatry*. 2006 Aug;67(8):1280-4.
- [24] Bakhireva LN, Schatz M, Chambers CD. Effect of maternal asthma and gestational asthma therapy on fetal growth. *J Asthma*. 2007 Mar;44(2):71-6.
- [25] Chambers C. Organization of Teratology Information Services (OTIS): Update and Direction. *Reproductive Toxicology*. 2004;19:239-60.
- [26] Ludowese CJ, Marini T, Laxova R, Pauli RM. Evaluation of the effectiveness of a teratogen information service: a survey of patient and professional satisfaction. *Teratology*. 1993;48(3):233-45.
- [27] Organization of Teratology Information Services. 2003-2004 Annual Report: Organization of Teratology Information Services; 2005.
- [28] Hoffmann C, Stoykova BA, Nixon J, Glanville JM, Misso K, Drummond MF. Do Health-Care Decision Makers Find Economic Evaluations Useful? The Findings of Focus Group Research in UK Health Authorities. *Value in Health*. 2002;5(2):71-8.
- [29] Pastuszak A, Bhatia D, Okotore B, Koren G. Preconception counseling and women's compliance with folic acid supplementation. *Can Fam Physician*. 1999;45:2053-7.
- [30] Einarson A SP, Koren G. Abrupt discontinuation of psychotropic drugs during pregnancy: Fear of teratogenic risk and impact of counselling. *Journal of Psychiatry & Neuroscience*. 2001 January 2001;26(1):44.

- [31] Ito S, Lieu M, Chan W, Koren G. Continuing drug therapy while breastfeeding. Part 1. Common misconceptions of patients. . *Can Fam Physician*. 1999;45:897-9.
- [32] Koren G, Bologna M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *American Journal of Obstetrics & Gynecology*. 1989;160:1190-4.
- [33] Einarson A, Lockett D. Do we have a knowledge transfer and translation plan at Teratogen Information Services? *Reproductive Toxicology*. 2006;22(3):542-5.
- [34] March of Dimes. Global Report on Birth Defects, The Hidden Toll of Dying and Disabled Children. White Plains, New York: March of Dimes Birth Defects Foundation; 2006.
- [35] Motherisk: Treating the mother, Protecting the Unborn [cited 2009 January 28]; Available from: [www.motherisk.org](http://www.motherisk.org)
- [36] Einarson A, Bailey B, Jung G, Spizzirri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. *Ann Allergy Asthma Immunol*. 1997;78:183-6.
- [37] Koren G, Pastuszak A. Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester. *Teratology*. 1990 Jun;41(6):657-61.
- [38] De Santis M, Straface G, Cavaliere A, Cinque B, Carducci B, Caruso A. Teratological risk evaluation and prevention of voluntary abortion. *Minerva Ginecol*. 2006;58(2):91-9.
- [39] Bailey B, Forget S, Koren G. Pregnancy outcome of women who failed appointments at a teratogen information service clinic. *Reproductive Toxicology*. 2002;16:77-80.
- [40] Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *The New England journal of medicine*. 1992 Dec 24;327(26):1832-5.
- [41] Mojtabai R. Body mass index and serum folate in childbearing age women. *European journal of epidemiology*. 2004;19(11):1029-36.
- [42] Wilson RD, Davies G, Desilets V, Reid GJ, Summers A, Wyatt P, et al. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can*. 2003 Nov;25(11):959-73.
- [43] de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Trends and predictors of folic acid awareness and periconceptional use in pregnant women. *American journal of obstetrics and gynecology*. 2005 Jan;192(1):121-8.
- [44] Johnson K, Posner SF, Biermann J, Cordero JF, Atrash HK, Parker CS, et al. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep*. 2006 Apr 21;55(RR-6):1-23.
- [45] Health Canada. Preconception Health: Folic Acid for the Primary Prevention of Neural Tube Defects. A Resource Document for Health Professionals.; 2002.

- [46] Goh YI, Bollano E, Einarson TR, Koren G. Prenatal Multivitamin Supplementation and Rates of Congenital Anomalies: A Meta-Analysis. *J Obstet Gynaecol Can* 2006;28(8):680-9.
- [47] Bower C, Miller M, Payne J, Serna P. Folate intake and the primary prevention of non-neural birth defects. *Australian and New Zealand journal of public health*. 2006 Jun;30(3):258-61.
- [48] Koren G, Piwko C, Ahn E, Boskovic R, Maltepe C, Einarson A, et al. Validation studies of the Pregnancy Unique-Quantification of Emesis (PUQE) scores. *J Obstet Gynaecol*. 2005 Apr;25(3):241-4.
- [49] Robbins JM, Cleves MA, Collins HB, Andrews N, Smith LN, Hobbs CA. Randomized trial of a physician-based intervention to increase the use of folic acid supplements among women. *American Journal of Obstetrics and Gynecology*. 2005;192:1126–32.
- [50] Kapur B, Koren G. Motherisk alert: Folic acid fortification of flour--three years later. *The Canadian journal of clinical pharmacology = Journal canadien de pharmacologie clinique*. 2001 Summer;8(2):91-2.
- [51] Abu-Hammad T, Dreier J, Vardy DA, Cohen AD. Physicians' knowledge and attitudes regarding periconceptional folic acid supplementation: a survey in Southern Israel. *Med Sci Monit*. 2008 May;14(5):CR262-7.
- [52] Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Annals of epidemiology*. 2003 May;13(5):317-24.
- [53] Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. *Immunology and allergy clinics of North America*. 2006 Feb;26(1):63-80.
- [54] Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006 Feb;61(2):169-76.
- [55] Bakhireva LN, Schatz M, Jones KL, Chambers CD. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol*. 2008 Aug;101(2):137-43.
- [56] Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. *British Medical Journal*. 2001 August 4;323:257-60.
- [57] Llewellyn AM, Stowe ZN, Nemeroff CB. Depression during pregnancy and the puerperium. *The Journal of clinical psychiatry*. 1997;58 Suppl 15:26-32.
- [58] Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. *Obstetrics and gynecology*. 2004 Apr;103(4):698-709.
- [59] Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *Journal of the American Medical Association*. 2006 February 1;295(5):499-507.

- [60] Orr ST JS, Prince CB. Maternal Prenatal Depressive Symptoms and Spontaneous Preterm Births among African-American Women in Baltimore, Maryland. *American Journal of Epidemiology*. 2002;156(9):797-802.
- [61] Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. *Journal of clinical epidemiology*. 1992 Oct;45(10):1093-9.
- [62] Lindahl V PJ, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health*. 2005;8:77-87.
- [63] Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use, in the ambulatory adult population of the United States: the Slone survey. *Journal of the American Medical Association*. 2002;287(3):337-44.
- [64] Svarstad BL, Cleary PD, Mechanic D, Robers PA. Gender differences in the acquisition of prescribed drugs: an epidemiological study. *Medical care*. 1987 Nov;25(11):1089-98.
- [65] Pole M, Einarson A, Paireudeau N, Einarson T, Koren G. Drug Labeling and Risk Perceptions of Teratogenicity: A Survey of Pregnant Canadian Women and Their Health Professionals. *Journal of Clinical Pharmacology*. 2000;40:573-7.
- [66] Statistics Canada. Employment by industry and sex. 2008 [cited 2009 Dec. 23]; Available from: <http://www40.statcan.gc.ca/l01/cst01/labor10a-eng.htm>
- [67] Khattak S, K-Moghtader M, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA*. 1999 Mar 24-31;281(12):1106-9.
- [68] The Motherisk Program Occupational/Environmental Exposures [cited July 5, 2006]; Available from: [www.motherisk.org](http://www.motherisk.org)
- [69] Schack-Nielsen L, Michaelsen KF. Breast feeding and future health. *Current opinion in clinical nutrition and metabolic care*. 2006 May;9(3):289-96.
- [70] Janke JR. The incidence, benefits and variables associated with breastfeeding: implications for practice. *The Nurse practitioner*. 1993 Jun;18(6):22-3, 8, 31-2.
- [71] Pugh LC, Milligan RA, Frick KD, Spatz D, Bronner Y. Breastfeeding duration, costs and benefits of a support program for low-income breastfeeding women. *Birth*. 2002;29:95-100.
- [72] Moretti ME, Lee A, Ito S. Which drugs are contraindicated during breastfeeding? Practice guidelines. *Can Fam Physician*. 2000 Sep;46:1753-7.
- [73] Elephant E, Boyer M, Boyer P, Galliot B, Roux C. Teratogenic Agent Information Centre: fifteen years of counseling and pregnancy follow-up. *Teratology*. 1992 Jul;46(1):35-44.
- [74] Fisk NM, Atun R. Market failure and the poverty of new drugs in maternal health. *PLoS medicine*. 2008 Jan 22;5(1):e22.
- [75] Addis A, Sharabi S, Bonati M. Risk Classification Systems for Drug Use During Pregnancy: Are They a Reliable Source of Information? *Drug Safety*. 2000;23(3):245-53.
- [76] Doering PL, Boothby LA, Cheek M. Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks? *American Journal of Obstetrics & Gynecology*. 2002 August 2002;187:333-9.

- [77] Widnes SK, Schjett J. Advice on Drug Safety in Pregnancy: Are there Differences between Commonly Used Sources of Information? *Drug Safety*. 2008;31(9):799-806.
- [78] Schwarz EB, Maselli J, Norton M, Gonzales R. Prescription of teratogenic medications in United States ambulatory practices. *The American Journal of Medicine* 2005;118:1240-9.
- [79] Malm H, Martikainen J, Klaukka T, Neuvonen PJ. Prescription of Hazardous Drugs During Pregnancy. *Drug Safety*. 2004;27(12):899-908.
- [80] Scialli AR, Buelke-Sam JL, Chambers CD, Friedman JM, Kimmel CA, Polifka JE, et al. Communicating risks during pregnancy: a workshop on the use of data from animal developmental toxicity studies in pregnancy labels for drugs. *Birth defects research*. 2004 Jan;70(1):7-12.
- [81] Kweder SL. Drugs and biologics in pregnancy and breastfeeding: FDA in the 21(st) century. *Birth defects research*. 2008 Sep;82(9):605-9.
- [82] Viguera AC CL, Bouffard S, Whitfield TH, Baldessarini RJ. Reproductive decisions by women with bipolar disorder after prepregnancy psychiatric consultation. *The American Journal of Psychiatry*. 2002;159(12):2102-4.
- [83] Garcia-Bournissen F, Tsur L, Goldstein LH, Staroselsky A, Avner M, Asrar F, et al. Fetal exposure to isotretinoin-an international problem. *Reproductive Toxicology*. 2008 Jan;25(1):124-8.
- [84] Koren G, Bologna M, Pastuszak A. Women's Perception of Teratogenic Risk. *Canadian Journal of Public Health*. 1991;82:S11-S4.
- [85] Einarson A, Park A, Koren G. How physicians perceive and utilize information from a teratogen information service: The Motherisk Program. *BMC Medical Education*. 2004 April 5;4(6).
- [86] Nevin AC, Parshuram C, Nulman I, Koren G, Einarson A. A survey of physicians' knowledge regarding awareness of maternal alcohol use and the diagnosis of FAS. *BMC Family Pract*. 2002;3.
- [87] Frost Widnes SK, Schjott J. Drug use in pregnancy--physicians' evaluation of quality and clinical impact of drug information centres. *European journal of clinical pharmacology*. 2009 Mar;65(3):303-8.
- [88] Einarson A, Schachtschneider AK, Halil R, Bollano E, Koren G. SSRI'S and other antidepressant use during pregnancy and potential neonatal adverse effects: Impact of a public health advisory and subsequent reports in the news media. *BMC Pregnancy and Childbirth*. 2005;5(11).
- [89] Lippman A, Houle E, Leclerc P. The role of the telephone in providing prenatal care. *American Journal of Preventative Medicine*. 1992;8(6):373-80.
- [90] Koeberl MK, Haun JM, Pauli RM. Temporal evolution of risk estimates for presumed human teratogens *Reproductive Toxicology*. 1993;7:343-8.
- [91] Bentur Y, Horlatsch N, Koren G. Exposure to ionizing radiation during pregnancy: perception of teratogenic risk and outcome. *Teratology*. 1991 Feb;43(2):109-12.
- [92] Koren G, Gladstone D, Robeson C, Robieux I. The perception of teratogenic risk of cocaine. *Teratology*. 1992;46:567-71.

- [93] Schaefer C, Hannemann D, Meister R. Post-marketing surveillance system for drugs in pregnancy—15 years experience of ENTIS. *Reproductive Toxicology*. 2005;20:331-43.
- [94] Kennedy D, Hurst V, Konradsdottir E, Einarson A. Pregnancy outcome following exposure to permethrin and use of teratogen information. *American journal of perinatology*. 2005 Feb;22(2):87-90.
- [95] Quinn D, Lavigne SV, Chambers C, Wolfe LJ, Chipman H, Cragan JD, et al. Addressing concerns of pregnant and lactating women after the 2005 hurricanes: the OTIS response. *The American Journal of Maternal/Child Nursing*. 2008;33(4):235-41.
- [96] Rimer BK, Gierisch JM. Public education and cancer control. *Seminars in oncology nursing*. 2005 Nov;21(4):286-95.
- [97] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 3 ed: Oxford University Press 2005.
- [98] Witney AG, Treharne GJ, Tavakoli M, Lyons AC, Vincent K, Scott DL, et al. The relationship of medical, demographic and psychosocial factors to direct and indirect health utility instruments in rheumatoid arthritis. *Rheumatology*. 2006;45:975-81.
- [99] Organisation for Economic Cooperation and Development (OECD). Health at a Glance - OECD Indicators 2005: OECD; 2005.
- [100] World Health Organization. Health topics - Health promotion. 2009 [cited 2009 Dec. 23]; Available from: [http://www.who.int/topics/health\\_promotion/en/](http://www.who.int/topics/health_promotion/en/)
- [101] Rush B, Shiell A, Hawe P. A census of economic evaluations in health promotion. *Health Education Research*. 2004;19(6):707-19.
- [102] Stone PW, Teutsch S, Chapman RH, Bell C, Goldie SJ, Neumann PJ. Cost-utility analyses of clinical preventive services: published ratios, 1976-1997. *Am J Prev Med*. 2000 Jul;19(1):15-23.
- [103] Belli PC, Bustreo F, Preker A. Investing in children's health: what are the economic benefits? *Bulletin of the World Health Organization*. 2005;83(10):777-84.
- [104] Grosse SD, Sotnikov SV, Leatherman S, Curtis M. The business case for preconception care: methods and issues. *Maternal and child health journal*. 2006 Sep;10(5 Suppl):S93-9.
- [105] Scheffler RM, Feuchtbaum LB, Phibbs CS. Prevention: the cost-effectiveness of the California Diabetes and Pregnancy Program. *Am J Public Health*. 1992 Feb;82(2):168-75.
- [106] Elixhauser A, Weschler JM, Kitzmiller JL, Marks JS, Bennert HW, Jr., Coustan DR, et al. Cost-benefit analysis of preconception care for women with established diabetes mellitus. *Diabetes care*. 1993 Aug;16(8):1146-57.
- [107] Herman WH, Janz NK, Becker MP, Charron-Prochownik D. Diabetes and pregnancy. Preconception care, pregnancy outcomes, resource utilization and costs. *J Reprod Med*. 1999 Jan;44(1):33-8.
- [108] Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003. *MMWR*. 2004 Jan 30;53(3):57-9.

- [109] Economic costs of birth defects and cerebral palsy--United States, 1992. *MMWR*. 1995 Sep 22;44(37):694-9.
- [110] Statistics Canada. Consumer Price Index, health and personal care. 2009 April 13 [cited 2009 July 27]; Available from: <http://www40.statcan.gc.ca/l01/cst01/econ161a-eng.htm>
- [111] Kirby RS, Brewster MA, Canino CU, Pavin M. Early childhood surveillance of developmental disorders by a birth defects surveillance system: methods, prevalence comparisons, and mortality patterns. *J Dev Behav Pediatr*. 1995 Oct;16(5):318-26.
- [112] Tilford JM, Robbins JM, Hobbs CA. Improving Estimates of Caregiver Time Cost and Family Impact Associated with Birth Defects. *Teratology*. 2001;64:S37-S41.
- [113] Grosse SD, Ouyang L, Collins JS, Green D, Dean JH, Stevenson RE. Economic evaluation of a neural tube defect recurrence-prevention program. *Am J Prev Med*. 2008 Dec;35(6):572-7.
- [114] Miller VL, Ransom SB, Ayoub MA, Krivchenia EL, Evans ME. Fiscal Impact of a Potential Legislative Ban on Second Trimester Elective Terminations for Prenatally Diagnosed Abnormalities. *American Journal of Medical Genetics*. 2000;91:359-62.
- [115] Waitzman NJ, Romano PS, Scheffler RM. Estimates of the economic costs of birth defects. *Inquiry*. 1994 Summer;31(2):188-205.
- [116] Lupton C, Burd L, Harwood R. Cost of Fetal Alcohol Spectrum Disorders. *American Journal of Medical Genetics Part C (Semin Med Genet)*. 2004;127C:42-50.
- [117] Stade B, Ungar WJ, Stevens B, Beyene J, Koren G. The burden of prenatal exposure to alcohol: measurement of cost. *JFAS International*. 2006;4(e5).
- [118] Klug MJ, Burd L. Fetal alcohol syndrome prevention: annual and cumulative cost savings. *Neurotoxicology and Teratology*. 2003;25:763-5.
- [119] Hopkins RB, Paradis J, Roshankar T, Bowen J, Tarride JE, Blackhouse G, et al. Universal or targeted screening for fetal alcohol exposure: a cost-effectiveness analysis. *Journal of studies on alcohol and drugs*. 2008 Jul;69(4):510-9.
- [120] Institute of Medicine. Preterm Birth: Causes, Consequences, and Prevention. Washington D.C.: Institute of Medicine; 2006.
- [121] Elliott C, Varon T. Containing Health Care Costs: The Effects of an Infant Wellness Program. *Health Marketing Quarterly*. 1995;12(4):63-75.
- [122] Lewit EM, Baker LS, Corman H, Shiono PH. The direct cost of low birth weight. *The future of children*. 1995;5(1):35-56.
- [123] Russell RB, Green NS, Steiner CA, Meikle S, Howse JL, Poschman K, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. *Pediatrics*. 2007 Jul;120(1):e1-9.
- [124] Tommiska V, Tuominen R, Fellman V. Economic costs of care in extremely low birthweight infants during the first 2 years of life. *Pediatr Crit Care Med*. 2003;4(2):157-63.
- [125] Lightwood JM, Phibbs CS, Glantz SA. Short-term health and economic benefits of smoking cessation: Low birth weight. *Pediatrics*. 1999;104(6):1312-20.

- [126] de Weerd S, Polder JJ, Cohen-Overbeek TE, Zimmermann LJ, Steegers EA. Preconception care: preliminary estimates of costs and effects of smoking cessation and folic acid supplementation. *J Reprod Med*. 2004;49(5):338-44.
- [127] Windsor RA, Lowe JB, Perkins LL, Smith-Yoder D, Artz L, Crawford M, et al. Health education for pregnant smokers: its behavioral impact and cost benefit. *American Journal of Public Health*. 1993;83(2):201-6.
- [128] Muender MM, Moore ML, Chen GJ, Sevick MA. Cost-benefit of a nursing telephone intervention to reduce preterm and low-birthweight births in an African American clinic population. *Preventive medicine*. 2000 Apr;30(4):271-6.
- [129] Parker DR, Windsor RA, Roberts MB, Hecht J, Hardy NV, Strolla LO, et al. Feasibility, cost, and cost-effectiveness of a telephone-based motivational intervention for underserved pregnant smokers. *Nicotine Tob Res*. 2007 Oct;9(10):1043-51.
- [130] Rigotti NA, Park ER, Regan S, Chang Y, Perry K, Loudin B, et al. Efficacy of telephone counseling for pregnant smokers: a randomized controlled trial. *Obstetrics and gynecology*. 2006 Jul;108(1):83-92.
- [131] Jentink J, van de Vrie-Hoekstra NW, de Jong-van den Berg LT, Postma MJ. Economic evaluation of folic acid food fortification in The Netherlands. *European journal of public health*. 2008 Jun;18(3):270-4.
- [132] Bentley TG, Weinstein MC, Willett WC, Kuntz KM. A cost-effectiveness analysis of folic acid fortification policy in the United States. *Public health nutrition*. 2009 Apr;12(4):455-67.
- [133] Postma MJ, Londeman J, Veenstra M, de Walle HEK, de Jong - van den Berg LTW. Cost-effectiveness of periconceptual supplementation of folic acid. *Pharm World Sci*. 2002;24(1):8-11.
- [134] Romano PS, Waitzman NJ, Scheffler RM, Pi RD. Folic acid fortification of grain: an economic analysis. *Am J Public Health*. 1995 May;85(5):667-76.
- [135] Llanos A, Hertrampf E, Cortes F, Pardo A, Grosse SD, Uauya R. Cost-effectiveness of a folic acid fortification program in Chile. *Health Policy*. 2007;83:295-303.
- [136] Sayed AR, Bourne D, Pattinson R, Nixon J, Henderson B. Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa. *Birth defects research*. 2008 Apr;82(4):211-6.
- [137] Grosse SD, Waitzman NJ, Romano PS, Mulinare J. Reevaluating the Benefits of Folic Acid Fortification in the United States: Economic Analysis, Regulation, and Public Health. *American Journal of Public Health*. 2005;95(11):1917-22.
- [138] Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. *Current medical research and opinion*. 2007 Apr;23(4):833-40.
- [139] Stray-Pedersen B, Jenum P. Economic evaluation of preventive programmes against congenital toxoplasmosis. *Scand J Infect Dis* 1992;Suppl. 84:86-96.
- [140] Cattaneo A, Ronfani L, Burmaz T, Quintero-Romero S, Macaluso A, Di Mario S. Infant feeding and cost of health care: A cohort study. *Acta Paediatrica*. 2006;95:540-6.

- [141] Ungar WJ. *Economic Evaluations in Child Health*. Oxford: Oxford University Press 2009.
- [142] Einarson A, Burt VK, Patroi D, Young B. Ruminative worrying during pregnancy: a case series. *J Obstet Gynaecol Can*. 2006 Aug;28(8):724-7.
- [143] Balken L, Martinez L, Grosse S. Building a Case for Funding a TIS From a Private Managed Care Organization in Utah. Organization of Teratology Information Specialists Annual Meeting; 2007; Monterey, CA; 2007.
- [144] Bashshur RL, Reardon TG, Shannon GW. Telemedicine: A new health care delivery system. *Annual Review of Public Health*. 2000;21(613-637):613.
- [145] May CR, Williams TL, Mair FS, Mort MM, Shaw NT, Gask L. Factors influencing the evaluation of telehealth interventions: preliminary results from a qualitative study of evaluation projects in the UK. *J Telemed Telecare*. 2002;8 Suppl 2:65-7.
- [146] Bunn F, Byrne G, Kendall S. Telephone consultation and triage: effects on health care use and patient satisfaction (Review). *The Cochrane Review*. 2004.
- [147] Hutti MH, Usui WM. Nursing Telephonic Case Management and Pregnancy Outcomes of Mothers and Infants. *Lippincott's Case Management*. 2004;9(6):287-99.
- [148] VanWormer JJ, Boucher JL, Pronk NP. Telephone-Based Counseling Improves Dietary Fat, Fruit, and Vegetable Consumption: A Best-Evidence Synthesis. *J Am Diet Assoc*. 2006;106:1434-44.
- [149] Nobili A, Gebru F, Rossetti A, Schettino F, Zahn RW, Nicolis E, et al. Doctorline: A Private Toll-free Telephone Medical Information Service. Five Years of Activity: Old Problems and New Perspectives. *The Annals of Pharmacotherapy*. 1998 January 1998;32:120-5.
- [150] Hagan L, Morin D, Lepine R. Evaluation of telenursing outcomes: satisfaction, self-care practices, and cost savings. *Public Health Nursing* 2000;17(4):305-13.
- [151] Hughes RA, Carr ME, Huggett A, Thwaites CEA. Review of the function of a telephone helpline in the treatment of outpatients with rheumatoid arthritis. *Ann Rheum Dis*. 2002;61:341-5.
- [152] Young TL, Ireson C. Effectiveness of School-Based Telehealth Care in Urban and Rural Elementary Schools. *Pediatrics*. 2003;112:1088-94.
- [153] O'Connell JM, Towles W, Yin M, Malakar CL. Patient Decision Making: Use of and Adherence to Telephone-Based Nurse Triage Recommendations. *Medical Decision Making*. 2002;22:309-17.
- [154] Hardyman R, Hardy P, Brodiea J, Stephens R. It's good to talk: comparison of a telephone helpline and website for cancer information. *Patient Education and Counseling*. 2005;57:315-20.
- [155] van Teijlingen ER, Hundley V, Rennie AM, Graham W, Fitzmaurice A. Maternity satisfaction studies and their limitations: "What is, must still be best". *Birth (Berkeley, Calif)*. 2003 Jun;30(2):75-82.
- [156] McIntosh E, Cairns J. A framework for the economic evaluation of telemedicine. *Journal of Telemedicine and Telecare*. 1997;3:132-9.

- [157] Johnson KA, Weber PA, Jones KL, Chambers CD. Selection Bias in Teratology Information Service Pregnancy Outcome Studies. *Teratology*. 2001;64:79-82.
- [158] Grossman M. On the Concept of Health Capital and the Demand for Health. *Journal of Political Economy*. 1972;80:223-55.
- [159] Bonari L, Koren G, Einarson TR, Jasper JD, Taddio A, Einarson A. Use of antidepressants by pregnant women: Evaluation of perception of risk, efficacy of evidence based counseling and determinants of decision making. *Archives of Women's Mental Health*. 2005;8:214-20.
- [160] Simon J, Petrou S, Gray A. The valuation of prenatal life in economic evaluations of perinatal interventions. *Health Econ*. 2009 Apr;18(4):487-94.
- [161] Donaldson C, Shackley P. Does "process utility" exist? A case study of willingness to pay for laparoscopic cholecystectomy. *Social Science & Medicine*. 1995;44(5):699-707.
- [162] Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: Beyond cost-effectiveness analysis. *Genetics in Medicine*. 2008;10(9):1-7.
- [163] Ryan M. Discrete choice experiments in health care. *British Medical Journal*. 2004 Feb 14;328(7436):360-1.
- [164] Louviere JJ, Hensher DA, Swait JD. Stated choice methods. Cambridge ; New York: Cambridge University Press 2000.
- [165] Louviere JJ, Hensher DA, Swait JD. Stated choice methods: analysis and application: Cambridge University Press 2000.
- [166] The Merriam-Webster Dictionary. 2 ed: Merriam-Webster Inc. 1993.
- [167] Ryan M, McIntosh E, Shackley P. Methodological issues in the application of conjoint analysis in health care. *Health Economics*. 1998;7:373-8.
- [168] Bryan S, Gold L, Sheldon R, Buxton M. Preference measurement using conjoint methods: an empirical investigation of reliability *Health Economics*. 2000;9:385-95.
- [169] Ryan M. Using conjoint analysis to take account of patient preferences and go beyond health outcomes: an application to in vitro fertilisation. *Social Science & Medicine*. 1999;48:535-46.
- [170] Bridges JFP. Stated preference methods in health care evaluation: an emerging methodological paradigm in health economics. *Applied Health Economics and Health Policy*. 2003;2(4):213-24.
- [171] Lee E, Maneno MK, Smith L, Weiss SR, Zuckerman IH, Wutoh AK, et al. National patterns of medication use during pregnancy. *Pharmacoepidemiology and Drug Safety*. 2006;15:537-45.
- [172] Kellett N, West F, Finlay AY. Conjoint analysis: a novel, rigorous tool for determining patient preferences for topical antibiotic treatment for acne. A randomised controlled trial. *British Journal of Dermatology*. 2006;154:524-32.
- [173] Fraenkel L, Bodarus S, Wittink DR. Understanding Patient Preferences for the Treatment of Lupus Nephritis With Adaptive Conjoint Analysis. *Medical Care*. 2001;39(11):1203-16.

- [174] Holt B, Morwitz VG, Ngo L, Harrison PF, Whaley KJ, Pettifor A, Nguyen AH. Microbicide Preference Among Young Women in California. *Journal of Women's Health*. 2006;15(3):281-94.
- [175] Newman PA, Duanb N, Lee SJ, Rudyc ET, Seiden DS, Kakinami L, et al. HIV vaccine acceptability among communities at risk: The impact of vaccine characteristics. *Vaccine*. 2006;24:2094-101.
- [176] Aristides M, Weston AR, FitzGerald P, Le Reun C, Maniadakis N. Patient Preference and Willingness-to-Pay for Humalog Mix25 Relative to Humulin 30/70: A Multicountry Application of a Discrete Choice Experiment. *Value in Health*. 2004 2004;7(4):442-54.
- [177] Sassi F, McDaid D, Ricciardi W. Conjoint analysis of preferences for cardiac risk assessment in primary care. *International Journal of Technology Assessment in Health Care*. 2005;21(2):211-8.
- [178] Lee L, Gin T, Lau ASC, Ng FF. A Comparison of Patients' and Health Care Professionals' Preferences for Symptoms During Immediate Postoperative Recovery and the Management of Postoperative Nausea and Vomiting. *Ambulatory Anesthesia*. 2005;100:87-93.
- [179] van den Berg B, Alb M, Brouwerb W, Exelb J, Koopmanschap M. Economic valuation of informal care: The conjoint measurement method applied to informal caregiving. *Social Science & Medicine*. 2005;61:1342-55.
- [180] Cote I, Gregoire JP, Moisan J, Chabot I, Lacroix G. A Pharmacy-Based Health Promotion Programme in Hypertension: Cost-Benefit Analysis. *Pharmacoeconomics*. 2003;21(6):415-28.
- [181] Dranitsaris G, Elia-Pacitti J, Cottrell W. Measuring Treatment Preferences and Willingness to Pay for Docetaxel in Advanced Ovarian Cancer. *Pharmacoeconomics*. 2004;22(6):375-87.
- [182] Lee P, Matchar DB, Clements DA, Huber J, Hamilton JD, Peterson ED. Economic Analysis of Influenza Vaccination and Antiviral Treatment for Healthy Working Adults. *Annals of Internal Medicine*. 2002;137:225-31.
- [183] Brent RJ. Cost-benefit analysis and health care evaluations: Edward Elgar Publishing Limited 2003.
- [184] Chung A, Macario A, El-Sayed YY, Riley ET, Duncan B, Druzin ML. Cost-Effectiveness of a Trial of Labor After Previous Cesarean. *Obstetrics & Gynecology*. 2001;97:932-41.
- [185] Mrus J, Goldie S, Weinstein M, Tsevat J. The cost-effectiveness of elective cesarean delivery for HIV-infected women with detectable HIV RNA during pregnancy. *AIDS*. 2000;14:2543-52.
- [186] Cote I, Gregoire JP, Moisan J, Chabot I, Lacroix G. A pharmacy-based health promotion programme in hypertension: cost-benefit analysis. *Pharmacoeconomics*. 2003;21(6):415-28.
- [187] Lee PY, Matchar DB, Clements DA, Huber J, Hamilton JD, Peterson ED. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. *Annals of internal medicine*. 2002 Aug 20;137(4):225-31.

- [188] Goodwin J, Rieder S, Rieder MJ, Matsui D. Counseling regarding pregnancy-related drug exposures by family physicians in Ontario. *Can J Clin Pharmacol*. 2007 e69;14(1):e58-e69.
- [189] Hancock RL, Koren G, Einarson A, Ungar WJ. The effectiveness of Teratology Information Services (TIS). *Reproductive Toxicology*. 2007;23(2):125-32.
- [190] Hancock RL, Ungar WJ, Einarson A, Goodstadt M, Koren G. Providing information regarding exposures in pregnancy: A survey of North American Teratology Information Services. *Reproductive Toxicology*. 2008;25(3):381-7.
- [191] Hancock RL, Koren G, Einarson A, Ungar WJ. International Practices in the Provision of Teratology Information: a Survey of International Teratogen Information Programs and Comparisons with the North American Model. *Journal of Evaluation in Clinical Practice*. 2009;In Press.
- [192] Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans: Medical Research Council of Canada; 2005.
- [193] Wessa P. Free Statistics Software, Office for Research Development and Education, version 1.1.23-r3. 2009 [cited February 27, 2009]; Available from: <http://www.wessa.net>
- [194] Einarson A, Langos R, Gallo M, Moretti M, McMartin K. Letter to the editor: risk perception. *Reproductive Toxicology*. 1996;10(2):165.
- [195] Pellerin P, Elefant E. [Medication and pregnancy counseling, an uncomfortable role for the retail pharmacists]. *Annales pharmaceutiques francaises*. 2004 Jul;62(4):253-9.
- [196] De Santis M, Cesari E, Ligato MS, Nobili E, Straface G, Cavaliere A, et al. Prenatal drug exposure and teratological risk: One-year experience of an Italian Teratology Information Service. *Med Sci Monit*. 2008;14(2):PH1-PH8.
- [197] Garbis JM, Robert E, Peters PW. Experience of two teratology information services in Europe. *Teratology*. 1990 Dec;42(6):629-34.
- [198] CORN. Framework for provision of Teratology Information Services. *Reproductive Toxicology*. 1994 Sep-Oct;8(5):439-42.
- [199] Keeton K, Hayward RA. Pregnancy intention and birth outcomes: does the relationship differ by age or race? *Journal of women's health (2002)*. 2007 May;16(4):510-6.
- [200] Schedule of Benefits for Physician Services under the Health Insurance Act: Ontario Ministry of Health and Long Term Care; 2008.
- [201] Childbirth, Connection. Planning Pregnancy: Genetic Counseling and Testing. <http://www.childbirthconnection.org/article.asp?ck=10310> January 16, 2009.
- [202] Clementi M, Di Gianantonio E. Teratogen Information Services: European Situation. NATO Advanced Research Workshop on "Drugs in Pregnancy: Consensus Conference on Teratogen Information Services"; 2004; Prague: *Reproductive Toxicology*; 2004. p. 240.
- [203] Chambers CD, Braddock SR, Briggs GG, Einarson A, Johnson YR, Miller RK, et al. Postmarketing Surveillance for Human Teratogenicity: A Model Approach. *Teratology*. 2001;64:252-61.

- [204] Toralles MB, Trindade BM, Fadul LC, Peixoto Junior CF, Santana MA, Alves C. [Importance of the Teratogen Information Service in Bahia, Brazil, for prevention of congenital malformations: an initial four-year review]. *Cadernos de saude publica / Ministerio da Saude, Fundacao Oswaldo Cruz, Escola Nacional de Saude Publica*. 2009 Jan;25(1):105-10.
- [205] Wyszynski DF. Pregnancy exposure registries: academic opportunities and industry responsibility. *Birth defects research*. 2009 Jan;85(1):93-101.
- [206] Denavas-Walt C, Proctor CB, Smith J. Income, Poverty, and Health Insurance Coverage in the United States: 2007. Washington, D.C.: U.S. Census Bureau; 2008.
- [207] Buekens P, Kotelchuck M, Blondel B, Kristensen FB, Chen JH, Masuy-Stroobant G. A comparison of prenatal care use in the United States and Europe. *Am J Public Health*. 1993 Jan;83(1):31-6.
- [208] Sayal K. Alcohol consumption in pregnancy as a risk factor for later mental health problems. *Evidence-based mental health*. 2007 Nov;10(4):98-100.
- [209] Szlemko WJ, Wood JW, Thurman PJ. Native Americans and alcohol: past, present, and future. *The Journal of general psychology*. 2006 Oct;133(4):435-51.
- [210] Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. *Reproductive Toxicology*. 1995 Jul-Aug;9(4):337-49.
- [211] Baye MR, Kovenock D, De Vries CG. Comparative analysis of litigation systems: an auction-theoretic approach. *The Economic Journal*. 2005;115(505):583-601.
- [212] Whitehead JC, Pattanayak SK, VanHoutven GL, Gelso BR. Combining Revealed and Stated Preference Data to Estimate the Non-market Value of Ecological Services: An Assessment of the State of the Science. *Journal of Economic Surveys*. 2008;22(5):872-908.
- [213] Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. *British Medical Journal*. 2000;320:1530-3.
- [214] Ryan M, Hughes J. Using conjoint analysis to assess women's preferences for miscarriage management. *Health Economics*. 1997;6:261-73.
- [215] SanMiguel F, Ryan M, McIntosh E. Applying conjoint analysis in economic evaluations: an application to menorrhagia. *Applied Economics*. 2000;32:823-33.
- [216] Longworth L, Ratcliffe J, Boulton M. Investigating women's preferences for intrapartum care: home versus hospital births. *Health and Social Care in the Community* 2001;9(6):404-13.
- [217] Hundley V, Ryan M, Graham W. Assessing women's preferences for intrapartum care. *Birth*. 2001;28(4):254-62.
- [218] McKessock L, Smith BH, Scott A, Graham W, Terry PB, Templeton A, et al. A randomized controlled trial of direct access for laparoscopic sterilization. *Family practice*. 2001 Feb;18(1):1-8.
- [219] Taylor S, Armour C. Consumer preference for dinoprostone vaginal gel using stated preference discrete choice modelling. *Pharmacoeconomics*. 2003;21(10):721-35.

- [220] Bishop AJ, Marteau TM, Armstrong D, Chitty LS, Longworth L, Buxton MJ, et al. Women and health care professionals' preferences for Down's Syndrome screening tests: a conjoint analysis study. *BJOG*. 2004 Aug;111(8):775-9.
- [221] Ryan M, Diack J, Watson V, Smith N. Rapid prenatal diagnostic testing for Down syndrome only or longer wait for full karyotype: the views of pregnant women. *Prenat Diagn*. 2005;25:1206-11.
- [222] Christofides NJ, Muirhead D, Jewkes RK, Penn-Kekana L, Conco DN. Women's experiences of and preferences for services after rape in South Africa: interview study. *British Medical Journal*. 2006;332:209-13.
- [223] Lewis S, Cullinane FM, Carlin JB, Halliday JL. Women's and health professionals' preferences for prenatal testing for Down syndrome in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2006;46:205-11.
- [224] Hall J, Fiebig DG, King MT, Hossain I, Louviere JJ. What influences participation in genetic carrier testing? Results from a discrete choice experiment. *J Health Econ*. 2006 May;25(3):520-37.
- [225] Wordsworth S, Ryan M, Skatun D, Waugh N. Women's preferences for cervical cancer screening: a study using a discrete choice experiment. *Int J Technol Assess Health Care*. 2006 Summer;22(3):344-50.
- [226] Basen-Engquist K, Fouladi RT, Cantor SB, Shinn E, Sui D, Sharman M, et al. Patient assessment of tests to detect cervical cancer. *Int J Technol Assess Health Care*. 2007 Spring;23(2):240-7.
- [227] Seston EM, Elliott RA, Noyce PR, Payne K. Women's preferences for the provision of emergency hormonal contraception services. *Pharm World Sci*. 2007;29:183-9.
- [228] Petrou S, McIntosh E. Women's Preferences for Attributes of First-Trimester Miscarriage Management: A Stated Preference Discrete-Choice Experiment. *Value Health*. 2008 Sep 16.
- [229] Pitchforth E, Watson V, Tucker J, Ryan M, van Teijlingen E, Farmer J, et al. Models of intrapartum care and women's trade-offs in remote and rural Scotland: a mixed-methods study. *BJOG*. 2008 Apr;115(5):560-9.
- [230] Bijlenga D, Birnie E, Bonsel GJ. Feasibility, Reliability, and Validity of Three Health-State Valuation Methods Using Multiple-Outcome Vignettes on Moderate-Risk Pregnancy at Term. *Value Health*. 2009 Mar 10.
- [231] Pavlova M, Hendrix M, Nouwens E, Nijhuis J, van Merode G. The choice of obstetric care by low-risk pregnant women in the Netherlands: Implications for policy and management. *Health Policy*. 2009 Jun 17.
- [232] Kruk ME, Paczkowski M, Mbaruku G, de Pinho H, Galea S. Women's preferences for place of delivery in rural Tanzania: a population-based discrete choice experiment. *American journal of public health*. 2009 Sep;99(9):1666-72.
- [233] Berwick DM, Weinstein MC. What do patients value? Willingness to pay for ultrasound in normal pregnancy. *Medical Care*. 1985;23(7):881-93.

- [234] Henry A, Crowther C. Sources of advice on medication use in pregnancy and reasons for medication uptake and cessation during pregnancy. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2000 May;40(2):173-5.
- [235] Hjelmgren J, Anell A. Population preferences and choice of primary care models: A discrete choice experiment in Sweden. *Health Policy*. 2007.
- [236] Scott A, Watson MS, Ross S. Eliciting preferences of the community for out of hours care provided by general practitioners: a stated preference discrete choice experiment. *Social Science & Medicine*. 2003;56:803-14.
- [237] Gerard K, Lattimer V, Surridge H, George S, Turnbull J, Burgess A, et al. The introduction of integrated out-of-hours arrangements in England: a discrete choice experiment of public preferences for alternative models of care. *Health Expect*. 2006 Mar;9(1):60-9.
- [238] Caldwell J, Bond C, Ryan M, Campbell NC, Miguel FS, Kiger A, et al. Treatment of minor illness in primary care: a national survey of patient satisfaction, attitudes and preferences regarding a wider nursing role. *Health Expect*. 2007 Mar;10(1):30-45.
- [239] Markham FW, Diamond JJ, Hermansen CL. The Use of Conjoint Analysis to Study Patient Satisfaction. *Evaluation and the Health Professions*. 1999;22:371-8.
- [240] Turner D, Tarrant C, Windridge K, Bryan S, Boulton M, Freeman G, et al. Do patients value continuity of care in general practice? An investigation using stated preference discrete choice experiments. *Journal of Health Services Research & Policy*. 2007;12(3):132-7.
- [241] Ratcliffe J, Buxton M. Patients' preferences regarding the process and outcomes of life-saving technology. *International Journal of Technology Assessment in Health Care*. 1999;15(2):340-51.
- [242] Phillips KA, Maddala T, Johnson FR. Measuring Preferences for Health Care Interventions Using Conjoint Analysis: An Application to HIV Testing. *Health Services Research*. 2002;37(6):1681-705.
- [243] Jan S, Mooney S, Ryan M, Bruggeman K, Alexander K. The use of conjoint analysis to elicit community preferences in public health research: a case study of hospital services in South Australia. *Australian and New Zealand Journal of Public Health*. 2000;24(1):64-70.
- [244] Wu G, Lancot KL, Herrmann N, Moosa S, Oh PI. The Cost-Benefit of Cholinesterase Inhibitors in Mild to Moderate Dementia: A Willingness-To-Pay Approach. *CNS Drugs*. 2003;17(14):1045-57.
- [245] Marra C, Frighetto L, Goodfellow AF, Wai AO, Chase L, Nicol RE, Leong CA, Tomlinson S, Ferreira BM, Jewesson PJ. Willingness to pay to assess patient preferences for therapy in a Canadian setting. *BMC Health Services Research*. 2005;5:43-9.
- [246] Sadri H, MacKeigan LD, Leiter LA, Einarson TR. Willingness to Pay for Inhaled Insulin: A Contingent Valuation Approach. *Pharmacoeconomics*. 2005;23(12):1215-27.
- [247] Bishai DM, Lang HC. The willingness to pay for wait reduction: the disutility of queues for cataract surgery in Canada, Denmark, and Spain. *J Health Econ*. 2000 Mar;19(2):219-30.

- [248] O'Brien BJ, Novosel S, Torrance G, Streiner D. Assessing the economic value of a new antidepressant. A willingness-to-pay approach. *Pharmacoeconomics*. 1995 Jul;8(1):34-45.
- [249] Alberini A, Krupnick A, Cropper ML, Simon NB, Cook J. The Willingness to Pay for Mortality Risk Reductions: A Comparison of the United States and Canada: SSRN 2001.
- [250] Pavlova M, Groot W, van Merode G. The importance of quality, access and price to health care consumers in Bulgaria: a self-explicated approach. *The International journal of health planning and management*. 2003 Oct-Dec;18(4):343-61.
- [251] Vick S, Scott A. Agency in health care. Examining patients' preferences for attributes of the doctor-patient relationship. *Journal of Health Economics*. 1998;17:587-605.
- [252] Longo MF, Cohen DR, Hood K, Edwards A, Robling M, Elwyn G, et al. Involving patients in primary care consultations: Assessing preferences using discrete choice experiments. *British Journal of General Practice*. 2006;56:35-42.
- [253] Asbury J. Overview of focus group research. *Qualitative Health Research*. 1995;5(4):414-20.
- [254] Tang KC, Davis A. Critical factors in the determination of focus group size. *Family Practice* 1995;12(4):474-5.
- [255] Doctokr Family Medicine. [cited 2009 February 13]; Available from: [www.doctokr.com](http://www.doctokr.com)
- [256] TelaDoc: Affordable Healthcare [cited 2009 February 13]; Available from: <http://www.teladoc.com/home.php>
- [257] Doctor on Call: America's Healthline. [cited 2010 January 15]; Available from: [www.doctoroncall.com](http://www.doctoroncall.com)
- [258] Hotel Docs. [cited 2009 February 11]; Available from: <http://www.hoteldocs.com/Home.html>
- [259] Haas M. The impact of non-health attributes of care on patients' choice of GP. *Australian Journal of Primary Health*. 2005;11(1):8.
- [260] Boksa P. Antidepressant use during pregnancy. *J Psych Neurosci*. 2001;26(1):17-9.
- [261] Patkar AA, Bilal L, Masand PS. Pharmacotherapy of depression in pregnancy. *Ann Clin Psychiatry*. 2004;16(2):87-100.
- [262] Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. *American journal of obstetrics and gynecology*. 2007 Jun;196(6):544 e1-5.
- [263] Lim JM, Sullivan E, Kennedy D. MotherSafe: review of three years of counselling by an Australian Teratology Information Service. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2009 Apr;49(2):168-72.
- [264] Farrar S, Ryan M. Response-ordering effects: a methodological issue in conjoint analysis. *Health Economics*. 1999;8:75-9.
- [265] Kjaer T, Bech M, Gyrd-Hansen D, Hart-Hansen K. Ordering effect and price sensitivity in discrete choice experiments: need we worry? *Health Econ*. 2006 Nov;15(11):1217-28.
- [266] Sawtooth. Choice Based Conjoint v. 6.0 Technical Paper. Sequim, WA: Sawtooth Software; 2008.

- [267] Ryan M, Skatun D. Modelling non-demanders in choice experiments. *Health Econ.* 2004 Apr;13(4):397-402.
- [268] Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. *Pharmacoeconomics.* 2008;26(8):661-77.
- [269] Brazell JD, Diener CD, Karniouchina E, Moore WL, Severin V, Uldry PF. The no-choice option and dual response choice designs. *Market Lett.* 2006;17:255-68.
- [270] Marshall DA, Johnson FR, Phillips KA, Marshall JK, Thabane L, Kulin NA. Measuring patient preferences for colorectal cancer screening using a choice-format survey. *Value in Health.* 2007;10(5):415-30.
- [271] Orme B. Sample Size Issues for Conjoint Analysis Studies: Sawtooth Software Inc.; 1998.
- [272] Ryan M, Gerard K. Using discrete choice experiments to value health care programmes: current practice and future research reflections. *Appl Health Econ Health Policy.* 2003;2(1):55-64.
- [273] Johnson RM, Orme BK. How Many Questions Should You Ask in Choice-Based Conjoint Studies?: Sawtooth Software Inc. Research Paper Series; 1996.
- [274] Huber J, Zwerina K. The importance of utility balance in efficient choice designs. *Journal of Marketing Research.* 1996;33(3):307-17.
- [275] Carlsson F, Martinsson P. Design techniques for stated preference methods in health economics. *Health Economics.* 2003;12:281-94.
- [276] Kuhfeld WF, Tobias RD, Garratt M. Efficient Experimental Design with Marketing Research Applications. *Journal of Marketing Research.* 1994;31:545-57.
- [277] Street DJ, Burgess L, Louviere JJ. Quick and easy choice sets: Constructing optimal and nearly optimal stated choice experiments. *Intern J of Research in Marketing.* 2005;22:459-70.
- [278] Ryan M, Bate A, Eastmond CJ, Ludbrook A. Use of discrete choice experiments to elicit preferences. *Qual Health Care.* 2001 Sep;10 Suppl 1:i55-60.
- [279] McTaggart-Cowan HM, Shi P, Fitzgerald JM, Anis AH, Kopec JA, Bai TR, et al. An evaluation of patients' willingness to trade symptom-free days for asthma-related treatment risks: a discrete choice experiment. *J Asthma.* 2008 Oct;45(8):630-8.
- [280] Sawtooth Software. 2009 [cited July 7, 2009]; Available from: [www.sawtoothsoftware.com](http://www.sawtoothsoftware.com)
- [281] UCLA: Academic Technology Services, Statistical Consulting Group. Introduction to SAS. [cited 2009 October 9]; Available from: <http://www.ats.ucla.edu/stat/sas/notes2/>
- [282] MetroNews. Metro News Toronto. 2009 [cited 2008 August]; Available from: <http://www.metronews.ca/toronto>
- [283] McDonald PW. A practical, cost-effective method for recruiting people into healthy eating behavior programs. *Prev Chronic Dis.* 2007;4(2):A26.
- [284] McIntosh S, Ossip-Klein DJ, Spada J, Burton K. Recruitment strategies and success in a multi-county smoking cessation study. *Nicotine Tob Res.* 2000;2(3):281-4.

- [285] Garrett SK, Thomas AP, Cicuttini F, Silagy C, Taylor HR, McNeil JJ. Community-based recruitment strategies for a longitudinal interventional study: the VECAT experience. *J Clin Epidemiol*. 2000;53(5):541-8.
- [286] Geraets JJ, de Groot IJ, Goossens ME, de Bruijn CP, de Bie RA, van den Heuvel WJ, et al. Comparison of two recruitment strategies for patients with chronic shoulder complaints. *Br J Gen Pract*. 2006;56(523):127-33.
- [287] Salim Silva M, Smith WT, Bammer G. Telephone reminders are a cost effective way to improve responses in postal health surveys. *J Epidemiol Community Health*. 2002;56(2):115-8.
- [288] Dillman DA. *Mail and Internet Surveys: the Tailored Design Method*: John Wiley & Sons. 2007.
- [289] Fredrickson DD, Jones TL, Molgaard CA, Carman CG, Schukman J, Dismuke SE, et al. Optimal design features for surveying low-income populations. *J Health Care Poor Underserved*. 2005;16(4):677-90.
- [290] Train K. *Discrete choice methods with simulation*. Cambridge, UK ; New York: Cambridge University Press 2003.
- [291] Greene WH. *Econometric analysis*. 5th ed. Upper Saddle River, N.J.: Prentice Hall 2003.
- [292] Amemiya T. Qualitative response models: a survey. *J Econ Lit*. 1981;19:1483-586.
- [293] McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, ed. *Frontiers in Econometrics*: Academic Press 1974.
- [294] Kuhfeld WF. *Multinomial logit, discrete choice modeling: An introduction to designing choice experiments, and collecting, processing, and analyzing choice data using SAS®*: SAS; 2002 August 31.
- [295] Hole AR. A comparison of approaches to estimating confidence intervals for willingness to pay measures. *Health Econ*. 2007 Aug;16(8):827-40.
- [296] Lancsar E, Louviere J. Deleting 'irrational' responses from discrete choice experiments: a case of investigating or imposing preferences? *Health Economics*. 2006;15:797-811.
- [297] Statistics Canada: Canada's National Statistics Agency. [cited 2009 January 28]; Available from: <http://www.statcan.gc.ca/start-debut-eng.html>
- [298] Beck CA, Patten SB, Williams JV, Wang JL, Currie SR, Maxwell CJ, et al. Antidepressant utilization in Canada. *Social psychiatry and psychiatric epidemiology*. 2005 Oct;40(10):799-807.
- [299] Cheraghi-Sohi S, Hole AR, Mead N, McDonald R, Whalley D, Bower P, et al. What Patients Want From Primary Care Consultations: A Discrete Choice Experiment to Identify Patients' Priorities. *Ann Fam Med*. 2008;6:107-15.
- [300] Rubin G, Bate A, George A, Shackley P, Hall N. Preferences for access to the GP: a discrete choice experiment. *British Journal of Family Practice*. 2006;56:743-8.
- [301] Gerard K, Salisbury C, Street D, Pope C, Baxter H. Is fast access to general practice all that should matter? A discrete choice experiment of patients' preferences. *J Health Serv Res Policy*. 2008 Apr;13 Suppl 2:3-10.

- [302] Gerard K, Lattimer V, Turnbull J, Smith H, George S, Brailsford S, et al. Reviewing emergency care systems 2: measuring patient preferences using a discrete choice experiment. *Emerg Med J*. 2004 Nov;21(6):692-7.
- [303] DiCenso A, Auffrey L, Bryant-Lukosius D, Donald F, Martin-Misener R, Matthews S, et al. Primary health care nurse practitioners in Canada. *Contemp Nurse*. 2007 Aug;26(1):104-15.
- [304] Kearley KE, Freeman GK, Heath A. An exploration of the value of the personal doctor-patient relationship in general practice. *Br J Gen Pract*. 2001 Sep;51(470):712-8.
- [305] Marmot MG. The Status Syndrome: how your social standing directly affects your health and life expectancy. London: Bloomsbury Pub. 2004.
- [306] Martinez-Frias ML. Problems of Using Data From Teratology Information Services (TIS) to Identify Putative Teratogens. *Teratology*. 1999;60:54-5.
- [307] Ornoy A, Mastroiacovo P. More on data from teratogen information systems (TIS). *Teratology*. 2000 May;61(5):327-8.
- [308] Gafni A. Alternatives to the QALY measure for economic evaluations. *Support Care Cancer*. 1997 Mar;5(2):105-11.
- [309] Bulik RJ. Human factors in primary care telemedicine encounters. *J Telemed Telecare*. 2008;14(4):169-72.
- [310] Cunningham CE, Deal K, Rimas H, Chen Y, Buchanan DH, Sdao-Jarvie K. Providing Information to Parents of Children with Mental Health Problems: A Discrete Choice Conjoint Analysis of Professional Preferences. *Journal of abnormal child psychology*. 2009 Jul 21.
- [311] Jung HP, Baerveldt C, Olesen F, Grol R, Wensing M. Patient characteristics as predictors of primary health care preferences: a systematic literature analysis. *Health Expect*. 2003 Jun;6(2):160-81.
- [312] Caruso EM, Rahnev DA, Banaji MR. Using Conjoint Analysis to Detect Discrimination: Revealing Covert Preferences from Overt Choices. *Social Cognition*. 2009;27(1):128-37.
- [313] McIntosh E, Ryan M. Using discrete choice experiments to derive welfare estimates for the provision of elective surgery: Implications of discontinuous preferences. *Journal of Economic Psychology*. 2002;23:367-82.
- [314] Skjoldborg US, Gyrd-Hansen D. Conjoint analysis. The cost variable: an Achilles' heel? *Health Economics*. 2003;12:479-91.
- [315] vanderPol M, Shiell A, Au F, Johnston D, Tough S. Convergent validity between a discrete choice experiment and a direct, open-ended method: comparison of preferred attribute levels and willingness to pay estimates. *Social science & medicine (1982)*. 2008 Dec;67(12):2043-50.
- [316] Ratcliffe J. The use of conjoint analysis to elicit willingness-to-pay values: Proceed With Caution? *International Journal of Technology Assessment in Health Care*. 2000;16(1):270-90.

- [317] Ryan M, Wordsworth S. Sensitivity of Willingness to Pay Estimates to the Level of Attributes in Discrete Choice Experiments. *Scottish Journal of Political Economy*. 2000;47(5):504-24.
- [318] Bryan S, Dolan P. Discrete choice experiments in health economics: For better or for worse? *Eur J Health Economics*. 2004;5:199-202.
- [319] McIntosh E, Donaldson C, Ryan M. Recent Advances in the Methods of Cost-Benefit Analysis in Healthcare: Matching the Art to the Science. *Pharmacoeconomics*. 1999;15(4):357-67.
- [320] Small KA, Rosen HS. Applied welfare economics with Discrete Choice Models. *Econometrica*. 1981;43(1):105-30.
- [321] Onwujekwe O, Dike N, Ojukwu J, Uzochukwu B, Ezumah N, Shu E, et al. Consumers stated and revealed preferences for community health workers and other strategies for the provision of timely and appropriate treatment of malaria in southeast Nigeria. *Malaria journal*. 2006;5:117.
- [322] Carlsson F, Martinsson P. Do hypothetical and actual marginal willingness to pay differ in choice experiments? *Journal of Environmental Economics and Management*. 2001;27:179-92.
- [323] Bhatia MR, Fox-Rushby JA. Willingness to pay for treated mosquito nets in Surat, India: the design and descriptive analysis of a household survey. *Health policy and planning*. 2002 Dec;17(4):402-11.
- [324] Telser H, Zweifel P. Validity of discrete-choice experiments evidence for health risk reduction. *Applied Economics*. 2007;39(1):69-78.
- [325] Salary Wizard. Salary Wizard 2009 [cited 2009 July 28]; Available from: <http://www.salary.com/>
- [326] Bank of Canada Financial Markets Dept. Annual Average of Exchange Rates. Ottawa: Bank of Canada; 2005.
- [327] Oracle Crystal Ball. [cited 2009 Sept. 14]; Available from: <http://www.oracle.com/crystalball/index.html>
- [328] Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ*. 1994 Mar-Apr;3(2):95-104.
- [329] Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC health services research*. 2006;6:52.
- [330] McIntosh E. Using Discrete Choice Experiments within a Cost-Benefit Analysis Framework. *Pharmacoeconomics*. 2006;24(9):855-68.
- [331] Dranitsaris G, Longo CJ, Grossman LD. The economic value of a new insulin preparation, Humalog Mix 25. Measured by a willingness-to-pay approach. *Pharmacoeconomics*. 2000 Sep;18(3):275-87.
- [332] Cook PF, Emiliozzi S, Waters C, El Hajj D. Effects of telephone counseling on antipsychotic adherence and emergency department utilization. *The American journal of managed care*. 2008 Dec;14(12):841-6.

- [333] Han J, Yang JH, Chung JH, Choi JS, Ahn HK, Ryu HM, Kim MY, Cho SI, Nava-Ocampo AA. Teratogen risk counselling by internet: A prospective cohort study. *Journal of Obstetrics and Gynaecology*. 2005;25(5):427-31.
- [334] Johnson B. Text messages could help turn the tide of HIV and AIDS in South Africa. *The Guardian*. 2008 Friday, October 24
- [335] Rosenfield A, Charo RA, Chavkin W. Moving forward on reproductive health. *The New England journal of medicine*. 2008 Oct 30;359(18):1869-71.
- [336] U.S. Food and Drug Administration. Guidance for Industry: Establishing Pregnancy Exposure Registries: US Department of Health and Human Services, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2002 Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf>. Accessed August 4, 2009.
- [337] Briggs GG, Polifka J. Better data needed from pregnancy registries. *Birth defects research*. 2009 Feb;85(2):109-11.
- [338] Archer NP, Langlois PH, Case AP, Wolfe LJ. Linking Teratogen Information Service and Birth Defects Registry Databases to Improve Knowledge of Birth Defect Status. *Birth Defects Research (Part A)*. 2006;76:126-8.
- [339] Birch S, Gafni A. The biggest bang for the buck or bigger bucks for the bang: the fallacy of the cost-effectiveness threshold. *Journal of health services research & policy*. 2006 Jan;11(1):46-51.
- [340] Towse A. Should NICE's threshold range for cost per QALY be raised? Yes. *British Medical Journal*. 2009;338:b181.
- [341] Birch S, Gafni A. Economics and the evaluation of health care programmes: generalisability of methods and implications for generalisability of results. *Health Policy*. 2003 May;64(2):207-19.
- [342] Birch S, Gafni A. Information created to evade reality (ICER): things we should not look to for answers. *Pharmacoeconomics*. 2006;24(11):1121-31.
- [343] Schackman BR, Oneda K, Goldie SJ. The cost-effectiveness of elective Cesarean delivery to prevent hepatitis C transmission in HIV-coinfected women. *AIDS*. 2004 Sep 3;18(13):1827-34.
- [344] Petrou S, Henderson J. Preference-based approaches to measuring the benefits of perinatal care. *Birth*. 2003 Dec;30(4):217-26.
- [345] Sackett K, Pope RK, Erdley WS. Demonstrating a positive return on investment for a prenatal program at a managed care organization. An economic analysis. *The Journal of perinatal & neonatal nursing*. 2004 Apr-Jun;18(2):117-27.
- [346] Lu MC, Lin YG, Prietto NM, Garite TJ. Elimination of public funding of prenatal care for undocumented immigrants in California: a cost/benefit analysis. *American journal of obstetrics and gynecology*. 2000 Jan;182(1 Pt 1):233-9.
- [347] International Society for Pharmacoeconomics and Outcomes Research Task Force: Good Research Practices for the Application of Conjoint Analysis in Health. 2009 [cited 2009

- Sept. 24, 2009]; Available from:  
<http://www.ispor.org/TaskForces/ConjointAnalysisGRP.asp>
- [348] Donnenfeld A, Hom M, Bandura B, Schick B. A subscription-generated revenue support program for a teratogen information service. *Reproductive toxicology (Elmsford, NY)*. 1996;10(2):163.
- [349] Ryan M. A role for conjoint analysis in technology assessment in health care? *Int J Technol Assess Health Care*. 1999;15(3):443-57.
- [350] Glanz K, Rimer BK, Lewis FM. Health behavior and health education : theory, research, and practice. 3rd ed. San Francisco: Jossey-Bass 2002.
- [351] U.S. Public Health Service. Risk Communication: Working With Individuals and Communities To Weigh the Odds. Prevention Report. Washington D.C. ; 1995.
- [352] O'Doherty K, Suthers GK. Risky communication: Pitfalls in counseling about risk, and how to avoid them. *Journal of Genetic Counseling*. 2007;16(4):409-17.
- [353] Sanz E, Gomez-Lopez T, Martinez-Quintas MJ. Perception of teratogenic risk of common medicines. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2001;95:127-31.
- [354] Ratnapalan S, Bona N, Chandra K, Koren G. Physicians' perceptions of teratogenic risk associated with radiography and CT during early pregnancy. *Ajr*. 2004 May;182(5):1107-9.
- [355] Alaszewski A, Horlick-Jones T. How can doctors communicate information about risk more effectively? *BMJ*. 2003 Sep 27;327(7417):728-31.
- [356] Edwards A, Hood K, Matthews E, Russell D, Russell I, Barker J, et al. The effectiveness of one-to-one risk communication interventions in health care: a systematic review. *Med Decis Making*. 2000 Jul-Sep;20(3):290-7.
- [357] Ontario Ministry of Health and Long-Term Care. Public Information. Telehealth Ontario. [cited 2009 Oct. 6, 2009]; Available from:  
<http://www.health.gov.on.ca/en/public/programs/telehealth/>
- [358] Rolland E, Moore KM, Robinson VA, McGuinness D. Using Ontario's "Telehealth" health telephone helpline as an early-warning system: a study protocol. *BMC health services research*. 2006;6:10.
- [359] van Dijk A, McGuinness D, Rolland E, Moore KM. Can Telehealth Ontario respiratory call volume be used as a proxy for emergency department respiratory visit surveillance by public health? *CJEM*. 2008 Jan;10(1):18-24.

## Appendices

### Appendix 1: Research Ethics Board Approval for Survey of Teratology Information Services

**Kids<sup>®</sup> Research Ethics Board (REB)**

*The REB is organized and operates according to the principles and practices stated in the Declaration of Helsinki, the Canadian Tri-Council Policy Statement (1998), ICH/GCP guidelines and Division 5 of the Food & Drug Regulations, Health Canada*

**Approval & Terms of Agreement**

Investigators: Dr. Wendy Ungar, G.Koren, A.Einarson

Project title: A survey of teratology information services (TIS)

File number: 1000009232

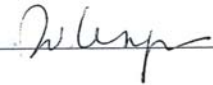
Protocol Version Date: May 30, 2006

Consent & Assent form version date:

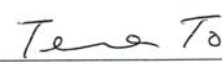
Investigator's Brochure version date:

Level of Continuing Review: I B


*I agree to carry out the proposed research involving human subjects in accordance with the protocol approved by the REB using the approved consent form/s. I shall notify the division/department head and the REB prior to implementing any amendments in the protocol and of any deviations, adverse or unexpected events as soon as possible. I certify that the research contract and corresponding protocol are consistent (where applicable) and will inform the contract manager of any proposed amendments.*

Signature of Primary Investigator  DATE 19 June 06

*I approve of this research protocol, agree to share responsibility for its proper conduct, and will ensure that the REB is notified of concerns, as appropriate.*

Signature of (Division/Department Head)  DATE June 19/2006

*The REB of the Hospital for Sick Children has reviewed and approved the above-named project.*



Dr. Melvin Freedman, REB Chair  
555 University Avenue  
Toronto, Ontario, M5G 1X8  
Tel: 416-813-6152  
Fax: 416-813-5085  
Email: [melvin.freedman@sickkids.ca](mailto:melvin.freedman@sickkids.ca)

DATE OF APPROVAL JUN 20 2006 EXPIRY DATE June 2007

## Appendix 2: Research Ethics Board Approval for Discrete Choice Survey

**SickKids** **Research Ethics Board (REB)**

*The Research Ethics Board for The Hospital for Sick Children is organized and operates according to the principles and practices outlined in the Tri-Council Policy Statement, the ICH Harmonized Tripartite Guidelines: Good Clinical Practice, and Division 5 and the Medical Devices Regulations of the Food and Drug Act as well as the Natural Health Products Regulations of Health Canada. This signed document is in lieu of the Health Canada Research Ethics Board Attestation Form.*

**Approval & Terms of Agreement**

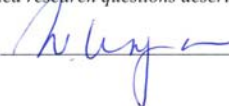
**Investigators:** Dr. Wendy Ungar, G.Koren, A.Einarson, R.Hancock

**Study Title:** Discrete Choice experiment to assess public Preferences & Willingness to Pay for Information Services During Pregnancy


**REB File number:** 1000011640 **Level of Continuing Review:** I B  
**Protocol Version Date:** October 4 2007  
**Consent & Assent Form Version Date(s):** Focus Group Consent Form- November 7 2007, Audio/Video Taping Consent Form- November 7 2007  
**Investigator's Brochure Version Date:** N/A  
**Other Approved Document Dates:** Study Questionnaire- October 4 2007

*I agree to carry out the proposed research involving human subjects in accordance with the above-noted guidelines and regulations (as applicable) and using only the REB-approved study protocol and consent/assent form(s). I shall notify the division/department head and the REB prior to implementing any amendments in the protocol and consent/assent forms and of any deviations or any changes in study activity. I shall also notify the REB of any unexpected adverse events as per REB guidelines. As applicable, I certify that the research contract and corresponding protocol are consistent and will inform the contract manager of any protocol amendments as required.*


*I agree that, in accordance with the Personal Health Information Protection Act of Ontario, I am responsible for adhering to all conditions and restrictions imposed by the REB governing the use, security, disclosure, return and disposal of the research subjects' personal health information. I am also responsible for reporting immediately any privacy breaches to the REB Chair and to Janice Campbell, the Sick Kids privacy officer. I will ensure that the personal health information is used, only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB.*

**Signature of Primary Investigator**  **DATE** 12 Nov 07

*I approve of this research protocol, agree to share responsibility for its proper conduct, and will ensure that the REB is notified of concerns, as appropriate.*

**Signature of Division/Department Head**  **DATE** Nov/12/2007

*The REB of the Hospital for Sick Children has reviewed and approved the above-named research study.*

  
**Dr. Melvin Freedman, REB Chair**  
 555 University Avenue, Toronto, Ontario, M5G 1X8  
 Tel: 416-813-6152 Fax: 416-813-5085 Email: [melvin.freedman@sickkids.ca](mailto:melvin.freedman@sickkids.ca)

**DATE OF APPROVAL** Nov 12 / 07 **EXPIRY DATE** Nov 2008

REB Form Version Date: 2007-05-29

## Appendix 3: List of Research Ethics Board Amendments

### **Survey of TIS**

#### Amendment 1

Date received: July 17, 2007

Date approved: Aug. 22, 2007

Reason: To expand the distribution of the survey from North American TIS to all TIS who would like to participate, globally.

### **Discrete Choice Experiment**

#### Amendment 1

Date received: Dec. 12, 2007

Date approved: Dec. 14, 2007

Reason: To increase the honorarium for focus group participants from a \$2 Tim Horton's gift card (which was given to survey respondents) to a \$20 Indigo gift card, to reflect their time and travel costs.

#### Amendment 2

Date received: Jan. 29, 2008

Date approved: April, 21, 2008

Reason: To allow for a fourth focus group discussion if desired; to increase the advertising budget.

#### Amendment 3

Date received: Aug. 12, 2008

Date approved: Aug. 12, 2008

Reason: Minor revisions were made to the consent letter to enhance readability.

#### Amendment 4

Date received: Sept. 29, 2008

Date approved: Oct. 3, 2008

Reason: To describe the provision of the survey online and the contract with Sawtooth Software to provide web hosting services. The consent letter was modified to reflect this change.

#### Amendment 5

Date received: Nov. 6, 2008

Date approved: Nov. 14, 2008

Reason: To expand the recruitment strategy to include other venues of advertisement such as community notice boards. The consent letter was modified to reflect this change.

## Appendix 4: Survey of Teratology Information Services (North American Version)

Version date: June 20, 2006

### Economic Evaluation of Teratology Information Services (TIS):

### SURVEY OF OTIS FACILITIES

Thank you for participating in our survey. This survey contains 34 questions in seven sections and should take approximately 15 minutes to complete. The sections are:

- I. DESCRIPTION OF RESPONDENT (3 questions)
- II. SERVICES (3 questions)
- III. STAFFING (5 questions)
- IV. OPERATIONS (13 questions)
- V. DATA COLLECTION (2 questions)
- VI. KNOWLEDGE TRANSFER ACTIVITIES (4 questions)
- VII. ADDITIONAL INFORMATION (4 questions)

The results of this survey will be used to create an economic model of teratology information services (TISs). You have been selected as a respondent as you are an administrator/director/employee of a teratology information service (TIS). All data collected will remain confidential and will not be shared. Individuals will not be identified within the database and all results will remain anonymous. Completion of the survey will serve as consent to participate.

The study coordinator is Rebecca Hancock, whom you may contact at the Hospital for Sick Children, Department of Population Health Sciences, telephone number 416-813-6978 and email address [rebecca.hancock@utoronto.ca](mailto:rebecca.hancock@utoronto.ca). If possible, please return the survey in person to Rebecca during the OTIS conference. If you require more time, a stamped, addressed envelope has been provided to you so that you return the survey by mail. You are making an invaluable contribution to this research project and we greatly appreciate your participation.

## SECTION I: DESCRIPTION OF RESPONDENT

Please answer the following questions about yourself in the event that we need to contact you for follow-up. This information will not be contained in any database.

1. i. Your name: \_\_\_\_\_

ii. Your telephone number: \_\_\_\_\_

iii. Your email address: \_\_\_\_\_

2. Role in organization: \_\_\_\_\_

3. What is the name & mailing address of your TIS?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**For Office Use Only:**

TIS number: \_\_\_\_\_

Date administered: \_\_\_\_\_

Date of follow-up: \_\_\_\_\_

Date completed: \_\_\_\_\_

Reviewed for completion (initials): \_\_\_\_\_

Date of data entry: \_\_\_\_\_

Data entry completed (initials): \_\_\_\_\_

## SECTION II: SERVICES

The questions in this section are about the services offered by your TIS.

*4. Which of the following are GOALS of your TIS? Please assign a level of importance from 1 (LEAST important) to 5 (MOST important) to each option. You may assign the same level of importance to more than one option.*

GOALS	Importance level
Correction of risk misperceptions & reassurance	
Counseling on exposures in lactation	
Education of other health professionals on teratology	
Prevention of Fetal Alcohol Syndrome (FAS) specifically	
Prevention of genetic malformations	
Prevention of malformations caused by exposure to teratogens	
Prevention of unnecessary pregnancy terminations due to high risk perception	
Support of adequate pharmacotherapy in pregnancy & lactation	
Other (please specify):	
Other (please specify):	
Other (please specify):	

5. What are the counseling information TOPICS offered by your service? Please allocate the percentage of your service's time spent counseling on these topics (to add up to 100%). Enter ZERO for those topics that do not apply to your TIS.

COUNSELING TOPIC	% of time
Alcohol	
Chemicals	
Drugs of abuse	
Environmental agents	
Exposures during lactation	
Exposures in the workplace	
Folic acid	
Genetics	
Herbal products	
Infections	
Medications	
Nausea & vomiting	
Smoking cessation	
Vaccinations	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100%</b>

6. What types of SERVICES do you offer? Please allocate the percentage of your service's time spent on each service (to add up to 100%). Enter ZERO for those options that do not apply to your TIS.

SERVICE	% of time
Clinic visits for women	
Diagnosis/testing of infants	
Education for other health care providers	
Genetic testing	
Material by fax for patient	
Material by fax for physician	
Material by mail for patient	
Material by mail for physician	
Telephone counseling	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100%</b>

### SECTION III: STAFFING

The questions in this section are about the number and types of staff that you employ at your service and other health care professionals that you may consult.

**7. What types of STAFF does your service employ? Please enter the number of Full Time Equivalents (FTE) for each category (e.g. part-time of 20 hours/week = 0.5 FTE; 2 full-time employees = 2 FTE). Enter ZERO for those not at your TIS.**

STAFF TYPE	FTE
Genetic counselors	
Nurses	
Managers/Directors	
Research assistants	
Secretaries	
Telephone counselors	
Toxicologists	
Volunteers	
Other (please specify):	
Other (please specify):	
Other (please specify):	

**8. What is the TOTAL NUMBER of paid employees (full-time and part-time) employed at your TIS?**

\_\_\_\_\_

9. What other types of HEALTH PROFESSIONALS are involved in providing services at your TIS? What type of ROLE do they play? (i.e. referral, consultation, research, patient care). If these people are paid, please circle HOW they are paid (fee for service=FFS, hospital staff salary=HSS, or other). Enter "N/A" for those not at your TIS.

HEALTH PROFESSIONAL	Role	Payment type (circle ONE)
Epidemiologists		FFS HSS Other
Geneticists		FFS HSS Other
Infectious disease specialists		FFS HSS Other
Obstetrician/gynecologists		FFS HSS Other
Paediatricians		FFS HSS Other
Pharmacists		FFS HSS Other
Toxicologists		FFS HSS Other
Other (please specify):		FFS HSS Other
Other (please specify):		FFS HSS Other
Other (please specify):		FFS HSS Other

10. What is the TOTAL NUMBER of health professionals who provide additional services at your TIS?

\_\_\_\_\_

11. Indicate the number of TRAINEES/STUDENTS in each category at your TIS. Enter ZERO for those not at your TIS.

TRAINEE/STUDENT	Number
Undergraduate student	
Masters student	

TRAINEE/STUDENT	Number
PhD student	
Medical student	
Pharmacy student	
Genetic counseling student	
Nursing student	
Clinical fellow	
Research fellow	
Post-doctoral fellow	
Other (please specify):	
Other (please specify):	
Other (please specify):	

## SECTION IV: OPERATIONS

12. i. In what kind of **INSTITUTION** are you situated? Please check **ONE**.

- Teaching hospital (i.e. university affiliated) → If YES, please complete part ii.
- Community hospital → If YES, please complete part ii.
- Public health unit
- Government health agency
- Physician's office
- Community health centre
- University (not affiliated with teaching hospital)
- Not-for-profit agency
- Other (please specify): \_\_\_\_\_
- Other (please specify): \_\_\_\_\_
- Other (please specify): \_\_\_\_\_

ii. If you are located within a hospital, in which **DEPARTMENT** are you located?

- Clinical pharmacology & toxicology
- Obstetrics and gynecology
- Pediatrics
- Other (please specify): \_\_\_\_\_
- Genetics
- Pharmacy
- Poison Control

13. Who **REFERS** clients to your service? Please allocate the percentage of your patients referred from each source (to add up to 100%). Enter **ZERO** for the options that do not apply to your **TIS**.

<b>REFERRAL SOURCE</b>	<b>%</b>
Abortion clinic	
Adoption program	
Advertising/self-promotion	
Family/friends	
Foster care program	
Internet	
Lactation consultants	
Media (TV, magazine, newspaper stories)	
Midwives	
Nurses	
Pharmacists	
Physicians	
Poison control centre	
Self-referral	
Substance abuse treatment program	
WIC program (supplementation plan for Women, Infants, Children)	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100%</b>

14. Identify the **GROUPS** of people whom you counsel. Please allocate the percentage of your counseling time devoted to each group (to add up to 100%). Enter **ZERO** for the options that do not apply to your TIS.

<b>GROUPS COUNSELED</b>	<b>% of time</b>
Pregnant women	
Women planning pregnancy	
Breast-feeding women	
Spouses/partners	
Physicians	
Pharmacists	
Nurses	
Lactation consultants	
Other health care providers	
Family members of pregnant women	
Family members of breast-feeding women	
Prospective adoptive parents	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100%</b>

15. On average, how many calls do you receive **WEEKLY**? (If less than one, please enter **ANNUAL** number of calls & specify that you are entering an annual number).

\_\_\_\_\_

16. On average, how long does each call last (**MINUTES**)?

\_\_\_\_\_

17. i. Do you perform follow-up calls?

- YES → If YES, please complete parts ii, iii, and iv.
- NO → If NO, please proceed to question 18 (page 10).

ii. If YES, are there **SPECIFIC** groups of callers whom you follow-up? Please describe:

\_\_\_\_\_

\_\_\_\_\_

iii. If YES, how long after the initial call will you typically follow-up (**DAYS**)?

\_\_\_\_\_

*iv. If YES, how many follow-up calls would you perform for a typical caller?*

\_\_\_\_\_

**18. i. Do you REFER callers to other physicians/services?**

- Yes → If YES, please complete part ii.
- No → If NO, please proceed to question 19 (page 11).

*ii. If YES, TO WHOM do you refer your callers? Please allocate the percentage of your referrals made to each category of physician/service (to add up to 100). Enter ZERO for the options that do not apply to your TIS.*

<b>REFERRALS</b>	<b>% of referrals</b>
Children's aid	
Genetic counselor	
Neonatologist	
Neurologist	
Obstetrician/gynecologist	
Paediatrician	
Perinatal psychiatrist	
Perinatologist	
Pharmacologist	
Psychologist	
Social services	
Sonologist (ultrasound)	
Toxicologist	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100</b>

**19. i. Do you assess a caller's risk perceptions or anxieties about exposure risks in your counseling?**

- Yes → If YES, please complete part ii.  
 No → If NO, please proceed to question 20 (this page).

**ii. If YES, please describe your methods of assessing a caller's anxiety.**

---



---

**20. On average, how many patients does your service counsel in person in CLINIC each week? Enter ZERO if this does not apply to your TIS.**

---

**21. i. What was your service's annual operating BUDGET in 2005?**

---

**ii. What cost items were included in your service's budget in 2005?**

- |   |  |
|---|--|
| <input type="radio"/> Salaries                                | <input type="radio"/> Equipment & supplies |
| <input type="radio"/> Telephone lines                         | <input type="radio"/> Capital & overhead   |
| <input type="radio"/> Database access                         | <input type="radio"/> Conference travel    |
| <input type="radio"/> Library services & journal subscription | <input type="radio"/> Research funding     |
| <input type="radio"/> Other (please specify): _____           |  |
| <input type="radio"/> Other (please specify): _____           |  |
| <input type="radio"/> Other (please specify): _____           |  |

**iii. What cost items were donated to your service in 2005?**

- |   |  |
|---|--|
| <input type="radio"/> Volunteer time                          | <input type="radio"/> Equipment & supplies |
| <input type="radio"/> Telephone lines                         | <input type="radio"/> Capital & overhead   |
| <input type="radio"/> Database access                         | <input type="radio"/> Conference travel    |
| <input type="radio"/> Library services & journal subscription | <input type="radio"/> Research funding     |
| <input type="radio"/> Other (please specify): _____           |  |
| <input type="radio"/> Other (please specify): _____           |  |
| <input type="radio"/> Other (please specify): _____           |  |

**22. How much SPACE does your service currently occupy? (square feet)**

23. How many of each of the following types of ROOMS do you have at your service?  
Enter ZERO for the options that do not apply to your TIS.

ROOM TYPE	Number
Administrative offices	
Clinic rooms for patient visits	
Telephone counseling rooms (Please enter the number of telephone counseling stations at your TIS: _____)	
Other (please specify):	
Other (please specify):	
Other (please specify):	

24. Indicate your sources of FUNDING. Please allocate percentage of total budget (to add up to 100%). Enter ZERO for the options that do not apply to your TIS.

FUNDING SOURCE	% total budget
Federal government	
State/Provincial government	
Municipal/Regional government	
Hospital budget	
Managed care organization	
Research grants	
Private donations	
Charitable organizations/foundations	
Fees charged to callers (If YES, please indicate the amount charged per caller: \$ _____)	
Other (please specify):	
Other (please specify):	
Other (please specify):	
<b>TOTAL</b>	<b>100%</b>

## SECTION V: DATA COLLECTION

The following questions are about the information your service collects from its callers.

**25. i. Does your service collect patient data?**

- YES → If YES, please complete parts ii and iii.
- NO → If NO, please proceed to question 26 (page 15).

**ii. What kinds of data do you collect? Please check all that apply and attach the INTAKE FORM you administer to your patients at the end of the survey.**

**Maternal baseline data**

- |   |   |
|---|---|
| <input type="radio"/> Weeks gestation                   | <input type="radio"/> Date of last menstrual period   |
| <input type="radio"/> Expected date of confinement      | <input type="radio"/> Gravidity/Parity                |
| <input type="radio"/> Ultrasound in current pregnancy   | <input type="radio"/> Defects in previous pregnancy   |
| <input type="radio"/> Medical problems                  | <input type="radio"/> Vitamin/mineral intake          |
| <input type="radio"/> Nausea & vomiting symptoms        | <input type="radio"/> Alcohol use                     |
| <input type="radio"/> Drug use                          | <input type="radio"/> Cigarette use                   |
| <input type="radio"/> Current medications               | <input type="radio"/> Current medication doses        |
| <input type="radio"/> History of current medication use | <input type="radio"/> Indication for medication       |
| <input type="radio"/> Method of referral to service     | <input type="radio"/> Paternal exposures              |
| <input type="radio"/> State/province of caller          | <input type="radio"/> Family history of birth defects |
| <input type="radio"/> Summary of information given      | <input type="radio"/> Occupation                      |

**General**

- |   |  |
|---|--|
| <input type="radio"/> Household income                  | <input type="radio"/> Address          |
| <input type="radio"/> Family set-up                     | <input type="radio"/> Pre-natal care   |
| <input type="radio"/> Use of other health care services | <input type="radio"/> Insurance status |

**Infant data**

- |   |  |
|---|--|
| <input type="radio"/> Birth date/ age           | <input type="radio"/> Birth weight             |
| <input type="radio"/> Gestational age           | <input type="radio"/> Apgar scores             |
| <input type="radio"/> Baby's general health     | <input type="radio"/> # times fed per 24 hours |
| <input type="radio"/> Supplemented with formula | <input type="radio"/> Age formula started      |
| <input type="radio"/> Supplemented with solids  | <input type="radio"/> Age solids started       |
| <input type="radio"/> Major malformations **    | <input type="radio"/> Minor malformations **   |

**\*\*If YES, please list the malformations you record:**

**Major malformations:**

---

---

**Minor malformations:**

---

---

**Other (please specify):**

---

---

---

***iii. Are your data maintained in a DATABASE?***

- Yes → If YES, please complete part iv.
- No → if NO, please proceed to part v.

***iv. Please provide details of how your data are stored and managed, such as number of computers, software used, mechanisms to ensure data security, etc.***

---

---

---

*v. Do you use these data for research purposes? If so, Please give three examples of research projects you have conducted and provide references if possible. If not, please proceed to question 26 (this page).*

1. \_\_\_\_\_  
\_\_\_\_\_

2. \_\_\_\_\_  
\_\_\_\_\_

3. \_\_\_\_\_  
\_\_\_\_\_

*26. i. Have you ever examined the costs of your service or performed any formal economic evaluations of your service?*

- YES → If YES, please complete part ii.  
 NO → If NO, please go to question 27 (this page).

*ii. If YES, please describe the costing studies or formal economic evaluations you have performed, and provide a reference if possible:*

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

## SECTION VI: KNOWLEDGE TRANSFER ACTIVITIES

The following questions are about your knowledge transfer activities.

*27. i. Does your service counsel health care providers?*

- YES → If YES, please complete part ii.  
 NO → If NO, please go to question 28 (page 16).

*ii. If YES, what PERCENTAGE of your calls are from health care providers? \_\_\_\_\_*

*28. i. Do members of your service participate in TRAINING other health care providers?*

- YES → If YES, please complete part ii.
- NO → If NO, please go to question 29 (page 16).

*ii. If YES, please describe your training activities:*

---



---



---

**29. i. Do members of your service make presentations to stakeholder groups?**

- YES → If YES, please complete part ii.
- NO → If NO, please go to question 30 (this page).

*ii. If YES, please indicate to which groups you have presented in the past year:*

- |   |   |
|---|---|
| <input type="radio"/> Health care providers         | <input type="radio"/> Patient groups          |
| <input type="radio"/> Hospital administrators       | <input type="radio"/> Women’s health groups   |
| <input type="radio"/> Government agencies           | <input type="radio"/> Community organizations |
| <input type="radio"/> Other (please specify): _____ |   |
| <input type="radio"/> Other (please specify): _____ |   |
| <input type="radio"/> Other (please specify): _____ |   |

**30. i. Does your service produce scientific research?**

- YES → If YES, please complete part ii, iii, & iv.
- NO → If NO, please go to question 31 (page 17).

*ii. How many scientific PAPERS has your group published?*

---

*iii. How many POSTERS has your group presented at scientific conferences in the last five years?*

---

*iv. How many ORAL PRESENTATIONS has your group given at scientific conferences in the last five years?*

---

## SECTION VII: ADDITIONAL INFORMATION

**31. If a person requiring teratology counseling was unable to access a TIS in your region or was unaware of the existence of the TIS, what OTHER INFORMATION RESOURCES are available to them? Please assign a level of importance for these resources in providing teratology information to people in your region from 1 (LEAST important) to 5 (MOST important). Enter "N/A" for those options that do not apply to your region.**

OTHER INFORMATION RESOURCES	Level of importance
Community health centre	
Family physician	
General telehealth line	
Genetic counselor (outside of TIS)	
Internet	
March of Dimes	
Media sources (e.g. TV, newspaper, magazines)	
Pharmaceutical company registry	
Poison control centre	
Public health office	
Other (please specify):	
Other (please specify):	
Other (please specify):	

**32. i. Does your service have a WEBSITE?**

- YES → If YES, please complete part ii.  
 NO → If NO, please go to question 33 (page 18).

**ii. If YES, please provide the URL (website address):**

---

**33. i. Have you ever completed any other surveys regarding your service?**

- Yes → If YES, please complete part ii.
- No → If NO, please go to question 34 (this page).

**ii. Please describe the nature and purpose of other surveys you have completed regarding your service.**

---

---

---

**FINALLY,**

**34. What other information can you provide that would be important in capturing the structure and function of a TIS?**

---

---

---

---

---

---

**Please attach a copy of your intake form and any descriptive literature you have on your service.**

THANK YOU FOR YOUR TIME

## Appendix 5: Consent Form for Focus Groups



THE HOSPITAL FOR  
SICK CHILDREN

Research Ethics Board

### **Title of Research Project**

**Focus Group Discussions to Inform a Conjoint Analysis Survey to Assess Public Preferences and Willingness to Pay for Teratogen Information Services**

### **Investigators:**

#### **Principal Investigator:**

Wendy Ungar, PhD

Telephone number: (416)813-7654 ext. 3487

#### **Co-Investigators:**

Gideon Koren, MD

Telephone number: (416)813-5781

Adrienne Einarson, RN

Telephone number: (416)813-4927

#### **Research Coordinator:**

Rebecca Hancock, MSc, PhD candidate (Supervisor: Dr. Wendy Ungar)

Telephone number: (416)813-5057

### **Purpose of the Research:**

There are few reliable sources of information on the safety or risk of medications and other types of exposures, such as infections, during pregnancy. Teratogen Information Services (TIS) are run by specialists in this field of medicine and provide this information over the telephone. The value of these services to the public has not been determined. We would like to determine what value the public places on these services and if they are considered to be different from a visit to a family doctor.

We would like to have discussions with TIS staff, TIS users, and women who have not used TIS in order to generate the best set of survey questions regarding the characteristics of TIS and family doctor visits.

### **Description of the Research:**

Research participants will be asked to attend a focus group discussion. These discussions should take approximately one hour. During the discussion, the research co-ordinator will ask questions and lead a discussion on what characteristics of a health service are important when pregnant women need information on medications. You will be asked to contribute to the discussion by giving your opinions and thoughts on the issues raised. There will be approximately 3-7 other participants in each group discussion. The discussion will be audio tape-recorded. To give your consent to being audio tape-recorded, a separate consent form will be completed.

**Potential Harms:**

We know of no harm that taking part in this study could cause you.

**Potential Discomforts or Inconvenience:**

We will ask you to travel to the hospital one time for the discussion group. We will ask you to stay at the discussion group meeting for up to two hours.

**Potential Benefits:*****To individual subjects:***

You will not benefit directly from participating in this study.

The results of the survey study that will be designed using data from the focus group discussions will eventually be published in a scientific journal. You may contact the research co-ordinator if you would like a copy of the survey study results.

***To society:***

The information that you provide will help us to conduct our research into people's preferences and willingness to pay for health care programs for pregnant women.

**Confidentiality:**

We will respect your privacy. No information about who you are will be given to anyone or be published without your permission, unless required by law.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data.

This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by Sick Kids policy.

Published study results will not reveal your identity.

During the group meeting we will remind everyone that the information shared is private and should not be repeated outside the group but we cannot be sure that information about you will be kept private. People in groups may share information with others outside the group.

**Reimbursement:**

We will compensate you for any travel expenses you have for coming to the hospital. To thank you for your time we will be giving you a \$20 gift certificate to Chapters.

**Participation:**

It is your choice to take part in this study. You can stop at any time. The care you get at Sick Kids will not be affected in any way by whether you take part in this study.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

During this study we may create new tests, new medicines, or other things that may be worth some money. Although we may make money from these findings, we cannot give you any of this money now or in the future because you took part in this study.

**Sponsorship:**

The sponsor/funder of this research is the Organization of Teratology Information Specialists and the Canadian Institute for Health Research.

**Conflict of Interest:**

I, and the other research team members have no conflict of interest to declare.

**Consent:**

By signing this form, I agree that:

- 1) You have explained this study to me. You have answered all my questions.
- 2) You have explained the possible harms and benefits (if any) of this study.
- 3) I know what I could do instead of taking part in this study. I understand that I have the right not to take part in the study and the right to stop at any time. My decision about taking part in the study will not affect my health care at Sick Kids.
- 4) I am free now, and in the future, to ask questions about the study.
- 5) I have been told that my medical records will be kept private except as described to me.
- 6) I understand that no information about who I am will be given to anyone or be published without first asking my permission.
- 7) I agree, or consent, to take part in this study.

\_\_\_\_\_  
Printed Name of Subject & Age

\_\_\_\_\_  
Subject's signature & date

\_\_\_\_\_  
Printed Name of person who  
explained consent

\_\_\_\_\_  
Signature of Person who  
explained consent & date

\_\_\_\_\_  
Printed Witness' name (if the subject/  
legal guardian does not read English)

\_\_\_\_\_  
Witness' signature & date

If you have any questions about this study, please call Rebecca Hancock at 416-813-6978.

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at 416-813-5718.

## Appendix 6: Audio Consent Form for Focus Groups

# SickKids®

THE HOSPITAL FOR  
SICK CHILDREN

Research Ethics Board

### **Video/audio taping & photography consent form**

#### **Title of Research Project:**

Focus Group Discussions to Inform a Conjoint Analysis Survey to Assess Public Preferences and Willingness to Pay for Teratogen Information Services

#### **Investigators:**

##### **Principal Investigator:**

Wendy Ungar, PhD

Telephone number: (416)813-7654 ext. 3487

##### **Co-Investigators:**

Gideon Koren, MD

Telephone number: (416)813-5781

Adrienne Einarson, RN

Telephone number: (416)813-4927

##### **Research Co-ordinator:**

Rebecca Hancock, MSc, PhD candidate (Supervisor: Dr. Wendy Ungar)

Telephone number: (416)813-5057

#### **Confidentiality:**

The pictures or tapes produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe the SickKids monitor, or employees of the company sponsoring the study or the regulator e.g., Health Canada) will have access to them. Following completion of the study the tapes/pictures will be kept as long as required in the SickKids “Records Retention and Destruction” policy. They will then be destroyed according to this same policy.

#### **Consent:**

By signing this form,

1) I also agree to be taped/photographed during this study. These tapes/photographs will be used to record a focus group discussion on attributes of teratogen information services and physician services for counseling on taking medications during pregnancy.

2) I understand that I have the right to refuse to take part in this study. I also have the right to withdraw from this part of the study at any time. eg., before or even after the tapes or photographs are made. My decision will not affect my health care at SickKids.

3) I am free now, and in the future, to ask questions about the taping/picture taking.

4) I have been told that my medical records will be kept private. You will give no one information about me, unless the law requires you to.

5) I understand that no information about me (including these tapes/pictures) will be given to anyone or be published without first asking my permission.”

6) I have read and understood pages 1 to 2 of this consent form. I agree, or consent, to having my picture taken/being taped as part of the study.

\_\_\_\_\_  
Printed Name of Subject & Age

\_\_\_\_\_  
Subject's signature & date

\_\_\_\_\_  
Printed Name of person who  
explained consent

\_\_\_\_\_  
Signature of Person who  
explained consent & date

\_\_\_\_\_  
Printed Witness' name (if the subject/  
legal guardian does not read English)

\_\_\_\_\_  
Witness' signature & date

In addition, I agree or consent for this tape(s)/photograph(s) to be used for:

1. Other studies on the same topic.
2. Teaching and demonstration at SickKids.
3. Teaching and demonstration at meetings outside SickKids.
4. Not to be used for anything else.

In agreeing to the use of the tape(s)/photograph(s) for other purposes, I have been offered a chance to view/hear the tape(s)/photograph(s). I also have the right to withdraw my permission for other uses of the tape(s)/photograph(s) at any time.

\_\_\_\_\_  
Printed Name of Subject & Age

\_\_\_\_\_  
Subject's signature & date

\_\_\_\_\_  
Printed Name of person who  
explained consent

\_\_\_\_\_  
Signature of Person who  
explained consent & date

\_\_\_\_\_  
Printed Witness' name (if the subject/  
legal guardian does not read English)

\_\_\_\_\_  
Witness' signature & date

## Appendix 7: Focus Group Discussion Questions

1. What are the values and benefits of asking a question at a family doctor's office?
2. What are the negative aspects of asking your question at a family doctor's office?
3. What are the values of benefits of asking a question over the telephone at a teratology information service?
4. What are the negative aspects of asking your question at a teratology information service?
5. What do you think are the most common questions people have during pregnancy?
6. What do you think are the most important questions people have during pregnancy?
7. What features would you like a health care service to have when you are asking questions/gathering information?
  - Over the phone
  - Doctor/other
  - Specific information
8. What would you be willing to pay for a consultation on your question if government/insurance didn't pay for it?
  - Range?
  - With a specialist
  - With a doctor
  - Over the telephone
9. Are you able to think about the cost to you without including other costs you might incur, such as travel, child care, and time away from work?
10. Other comments?

## Appendix 8: Focus Group Attribute Rating Form

<b>Attribute</b>	<b>Score (0=not important, 10=extremely important)</b>
<i>Person you contact</i>	
<i>Method of contact</i>	
<i>Waiting time</i>	
<i>Cost to you</i>	
<i>Helpfulness of advice provided</i>	
<i>Information provider's knowledge of your personal medical history</i>	
<i>Trust of information provider</i>	
<i>Time available for your consultation</i>	
<i>Specialization of information provider</i>	
<i>Education/training of information provider</i>	
<i>Ease of follow-up</i>	
<i>Able to provide specific research study data on topic of interest</i>	
<i>Comments/Other</i>	

## Appendix 9: Newspaper Advertisement for Discrete Choice Survey

### **Your Opinions Wanted for Research Study on Counseling About Risks During Pregnancy**

We are looking for men and women of all backgrounds aged 18 to 65 years to complete a survey online or by mail. The survey will ask you about what health care services you would prefer to use when you require information and counseling about using medications during pregnancy.

If you would like to participate or receive further information please contact the research coordinator:

Rebecca

Telephone: 416-813-5057

Email: [preference.study@gmail.com](mailto:preference.study@gmail.com)

*This study has received approval from the Hospital for Sick Children Research Ethics Board*

The logo for SickKids, featuring the word "SickKids" in a blue, sans-serif font. The "i" in "Sick" has a red dot, and the "s" in "Kids" has a red dot. The logo is set against a white background with a light blue shadow effect.

## Appendix 10: Discrete Choice Survey Consent Letter

### **Research Project Title: Public Preferences and Willingness to Pay for Health Care Services in Pregnancy**

Dear Study Participant,

The Hospital for Sick Children (Sick Kids) is studying preferences for health care information services during pregnancy. This letter will explain to you the purpose of our research study and how it is conducted. You have received this package as you have previously contacted us and said you were interested in our study, and you are also eligible for the study. Thank you for your interest and the time you have given to us. Please read this letter first. If you agree to be part of our study, please complete the survey. You were given two options for completing the survey, by mail or on-line. If you chose to complete the survey on paper, please fill out the attached survey and return it to us in the mail in the stamped envelope provided. If you chose to complete it on-line, please go to <http://www.preferencestudy.com> and follow the instructions for completion. Your user name is included with this letter. You will need this user name to log in to the survey web page. By completing and submitting the survey you are saying that you have read this letter and agree to be a participant in the study.

#### **Why are we conducting this study?**

There are few reliable sources of information on the safety or risk of using medications and many other risks during pregnancy. Pregnancy Risk Information Services are run by information specialists in this field of medicine (*teratology*) and provide information over the telephone. The value of these services to the public has not been determined. We would like to know what value the public places on these services and if they are considered to be different from a visit to a family doctor.

#### **What does the study involve?**

##### ***Your participation is voluntary***

You responded to one of our advertisements and contacted the study coordinator for more information. After receiving a description of the study, you agreed to participate and were mailed this study package, which contains this letter, the survey, and a stamped envelope for returning

the survey (or a user name if you are completing the survey online). If you still agree to participate after reading this letter, please complete the survey. If you do not agree, do not complete the survey.

### ***The survey***

The survey asks you to make choices between two possible health services you could use to get more information about using an anti-depressant medication during pregnancy. As you complete the survey, we ask you to imagine that you or your partner is pregnant and wants more information about using an anti-depressant medication through the pregnancy. In each question, the characteristics of the health care service options will be changed, and you will be asked to choose again between the different health care services. After the choice questions, there are 20 personal questions. The survey could take up to thirty minutes to complete.

If the survey is not returned within 3 weeks, the study coordinator will contact you to remind you about the survey and ask if you have any questions about it. If the survey is not returned after another 3 weeks, you will receive a second reminder telephone call. If the survey is not returned after the second reminder telephone call, we will assume that you are not interested in participating in the study and will not call you again.

### **Your privacy and confidentiality**

We respect your privacy. Each survey is given a study number (and user name for online respondents) so your name, address, and telephone number are not attached to the completed survey. Your personal information is only recorded in a study binder, kept in a locked office. The information collected in this survey will not be used for any other purpose. No information about who you are will be given to anyone or be published without your permission, unless required by law. The data produced from this study will be stored in a secure, locked location. Only members of the research team will have access to the data. This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by Sick Kids policy. Published study results will not reveal your identity.

### **What are the potential benefits and harms of participating in the study?**

Participants in this survey will have made an important contribution to scientific research. We know of no harm that taking part in this study could cause you. The results of this study may help us plan health care information services for pregnant women. As thanks for your time, we have included a \$2 gift card for Tim Horton's in the study package.

### **What happens if you change your mind about participating in the study?**

You choose to take part in this study. You can stop at any time. The care you get at Sick Kids will not be affected in any way whether you take part in this study or not.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

### **Will you be able to see the results of the study?**

We would like to share the findings of the study with you. Once the study is completed the findings will be posted on the Motherisk website at [www.motherisk.org](http://www.motherisk.org).

### **Who is conducting this study?**

The Principal Investigator has received financial support from the Canadian Institute for Health Research and the Organization of Teratology Information Specialists.

### **Who do you contact if you have questions about the study?**

Please contact us if you have any questions at any time.

#### ***Study Coordinator:***

Rebecca Hancock, MSc, PhD candidate (Supervisor: Dr. Wendy Ungar)  
Telephone number: (416)813-5057  
Email: [preference.study@gmail.com](mailto:preference.study@gmail.com)

#### ***Principal Investigator:***

Wendy Ungar, PhD  
Telephone number: (416)813-7654 ext. 3487

You may also contact the Hospital for Sick Children's Research Ethics Manager: Telephone number: (416)813-5718

## Appendix 11: Discrete Choice Survey (Version 1)

### INTRODUCTION TO THE SURVEY

**\*Please read this section before starting.**

The goal of our survey is to determine what characteristics of a health care service are important to you when you need counseling and information about the safety of using medications during pregnancy. When completing the survey, we ask you to imagine that you would like more information about the safety or risks of using an anti-depressant medication during pregnancy (this scenario will be described in more detail later on).

We will present a description of two different health care service options that you could use to get more information about using the medication during the pregnancy. The two options are described by six different characteristics. The characteristics will be slightly different in each question. First read the description of the two health care services and then check whether you would choose option A or option B. *There are no right or wrong choices.* We are interested in knowing what you would choose in *real life*. Your answers will help us to understand which characteristics of health care services are important to the public and will ultimately help to provide better health care during pregnancy. For the first fifteen questions, you will be making choices between two different health care service options. You will then be asked 20 personal questions.

The health care services will differ according to the six characteristics described below:

#### **1. Type of training of the information provider**

The information provider is the person who will provide the counseling and information about using the medication during pregnancy. The information provider will be either: (i) a *counselor with specialized training in use of medications during pregnancy only*, **or** (ii) a *family doctor with general health training*.

#### **2. Method of counseling and waiting time**

To receive the counseling and information you will either: (i) *make an appointment and meet with the information provider in person in 3 days*, **or** (ii) *call a telephone service and receive the information within 30 minutes*.

**3. Knowing the information provider**

Either: (i) *you have met the information provider before and they know your medical history, or* (ii) *the information provider is not known to you.*

**4. Confidence in the skills of the information provider**

Either: (i) *you have confidence in the skills of the information provider, or* (ii) *you are unaware of the skills of the information provider.*

**5. Helpfulness of counseling and information**

The counseling and information provided to you will either be: (i) *Very helpful: you understand the information provided to you and you feel your question has been answered to your satisfaction, or* (ii) *Somewhat helpful: Some information has been provided to you but you feel your question has not been completely answered to your satisfaction.*

**6. Cost to you**

This refers to how much money you would have to pay out of your own pocket to use the service. For the purposes of our survey, we are imagining that the cost of using the service would not be covered by insurance or the public health care system. This cost refers only to the amount of money that would come out of your pocket for using the service. The three options are \$10, \$50, and \$90. This cost does not include any other costs you may have, such as time away from work, travel to the appointment, etc. Please know that there are no plans to introduce user fees for these health services. However, one of the goals of this research study is to determine how much people value different services and one way to do this is to ask how much you would pay in an imaginary situation.

**All other characteristics of the services are the same.**

**The survey should take about thirty minutes to complete.**

**If you have any questions about the survey please contact Rebecca at 416-813-5057.**

**Please tell us a bit about yourself before starting:****What is your current age? \_\_\_\_\_** Prefer not to answer**What is your gender?** Female Male Prefer not to answer**What are the first 3 digits of your postal code? \_\_\_\_\_****BACKGROUND**

**\*Read this before starting. If you are male please imagine this statement is referring to your female partner:**

*Imagine that you were diagnosed with major depression one year ago. Being depressed meant that you had a depressed mood, disturbed sleep, loss of appetite, and a loss of pleasure in your regular activities for at least two weeks at a time. Your doctor prescribed an anti-depressant medication for you, which has made you feel much less depressed, and you have been taking it for about one year. You have just discovered that you are about six weeks pregnant. You are worried that your anti-depressant medication may be harmful to the baby. However, you are also afraid to stop taking the medication because being depressed makes you feel terrible, both physically and mentally. You would like more information about using your anti-depressant while you are pregnant.*

**START HERE:**

You can use one of two health services to get more information about using your anti-depressant while you are pregnant.

**1. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
The information provider is not known to you	You have met the information provider before and they know your medical history
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$90	\$50

Check ONE box only:


**2. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
You have met the information provider before and they know your medical history	The information provider is not known to you
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$10	\$50

Check ONE box only:

**3. If these were your only options, which would you choose?**

OPTION A	OPTION B
Family doctor with general health training	Counselor with specialized training in use of medications during pregnancy only
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$10	\$90

Check ONE box only:



**4. If these were your only options, which would you choose?**

OPTION A	OPTION B
Family doctor with general health training	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$90	\$10

Check ONE box only:

**5. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
\$50	\$90

Check ONE box only:



**6. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
\$10	\$90

Check ONE box only:

**7. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
You have met the information provider before and they know your medical history	The information provider is not known to you
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$50	\$10

Check ONE box only:



**8. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
\$50	\$10

Check ONE box only:

**9. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$50	\$10

Check ONE box only:



**10. If these were your only options, which would you choose?**

OPTION A	OPTION B
Family doctor with general health training	Counselor with specialized training in use of medications during pregnancy only
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$50	\$90

Check ONE box only:

**11. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
You have met the information provider before and they know your medical history	The information provider is not known to you
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$10	\$90

Check ONE box only:



**12. If these were your only options, which would you choose?**

OPTION A	OPTION B
Family doctor with general health training	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Make an appointment and meet with the information provider in person in 3 days
The information provider is not known to you	You have met the information provider before and they know your medical history
You are unaware of the skills of the information provider	You have confidence in the skills of the information provider
Some information has been provided to you but your question has not been completely answered to your satisfaction	Enough information has been provided that you feel your question has been answered to your satisfaction
\$90	\$10

Check ONE box only:

**13. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Call a telephone service and receive the information within 30 minutes	Make an appointment and meet with the information provider in person in 3 days
You have met the information provider before and they know your medical history	The information provider is not known to you
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
\$50	\$90

Check ONE box only:



**14. If these were your only options, which would you choose?**

OPTION A	OPTION B
Counselor with specialized training in use of medications during pregnancy only	Family doctor with general health training
Make an appointment and meet with the information provider in person in 3 days	Call a telephone service and receive the information within 30 minutes
The information provider is not known to you	You have met the information provider before and they know your medical history
You have confidence in the skills of the information provider	You are unaware of the skills of the information provider
Enough information has been provided that you feel your question has been answered to your satisfaction	Some information has been provided to you but your question has not been completely answered to your satisfaction
\$90	\$10

Check ONE box only:





**22. Do you have your own family doctor?**

- Yes
- No

**23. Do you think a telephone information service that provides counseling on the safety of medications during pregnancy should be available to the public?**

- Yes
- No
- Unsure

*Sometimes a person's background or previous experiences has an effect on their opinions. We will use the answers to the questions below to see if they have an effect on the choices you have made and to see if the sample of people who have completed this survey represents the general public. As with everything you tell us, we will keep this information strictly confidential and it will only be used for the purposes of this study.*

**24. Are you currently using any anti-depressant medication?**

- Yes
- No
- Prefer not to answer

**25. Are you or your partner currently pregnant?**

- Yes
- No
- Prefer not to answer

**26. Have you had any children?**

- Yes → If YES, please complete questions 27 and 28.
- No → If NO, please skip ahead to question 29.
- Prefer not to answer → Please skip ahead to question 29.

**27. How many children have you had? \_\_\_\_\_**

**28. Have you had any children with a birth defect?**

- Yes
- No

**29. Do you have any close friends or relatives who have had a child with a birth defect?**

- Yes  
 No  
 Prefer not to answer

**30. What is the highest level of schooling you have completed? Please check ONE:**

<input type="radio"/>	Less than high school
<input type="radio"/>	High school graduate
<input type="radio"/>	Some college or university
<input type="radio"/>	College or university graduate (e.g. bachelor's degree)
<input type="radio"/>	Post-graduate training (e.g. master's, post-graduate certificates)
<input type="radio"/>	Prefer not to answer

**31. What is your employment status? Please check ONE:**

<input type="radio"/>	Self-employed
<input type="radio"/>	Employed (full-time or part-time)
<input type="radio"/>	Unemployed
<input type="radio"/>	Student or full-time homemaker
<input type="radio"/>	On disability or social assistance
<input type="radio"/>	Other - please specify: _____
<input type="radio"/>	Prefer not to answer

**32. What language is most commonly spoken in your home?**

- English  
 French  
 Other - please specify: \_\_\_\_\_  
 Prefer not to answer

**33. What is your ethnic background? Please check all that you feel apply:**

<input type="checkbox"/>	Caucasian
<input type="checkbox"/>	African
<input type="checkbox"/>	Asian
<input type="checkbox"/>	Other – please specify: _____
<input type="checkbox"/>	Prefer not to answer

**34. Were you born in Canada?**

- Yes  
 No  
 Prefer not to answer

**35. What is your gross (before taxes) annual household income? Please check ONE:**

<input type="checkbox"/>	\$0-30,000
<input type="checkbox"/>	\$30,000-40,000
<input type="checkbox"/>	\$40,000-50,000
<input type="checkbox"/>	\$50,000-60,000
<input type="checkbox"/>	\$60,000-70,000
<input type="checkbox"/>	\$70,000-80,000
<input type="checkbox"/>	Over \$80,000
<input type="checkbox"/>	Prefer not to answer

**THE END**

*Thank you very much for taking the time to complete our survey!*

Please mail the completed survey back to us in the stamped envelope provided.

### Appendix 12: Distributions for Incremental Benefits and Incremental Costs in the Cost-Benefit Analysis

