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UMI
ASSESSMENT OF THE EFFECTS OF RISK-COUNSELLING (MOTHERISK) ON PRESCRIPTION MEDICATION SELF-MANAGEMENT PRACTICES- AN EXPLORATORY STUDY

BY

COLLEEN S. DUNCAN

A THESIS SUBMITTED IN CONFORMITY WITH THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE GRADUATE DEPARTMENT OF PHARMACEUTICAL SCIENCES UNIVERSITY OF TORONTO

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Signed: Colleen Quinn
ABSTRACT

Assessment of the effects of risk-counselling (Motherisk) on prescription medication self-management practices- an exploratory study.

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Objectives: To investigate the effects of Motherisk-counselling on factors hypothesized to influence attitudes towards medication usage intentions and Drug Therapy Self Management of pregnant women callers. To develop a survey instrument with quantitative and qualitative elements.

Design: Non-experimental, one-group pretest-posttest.

Setting: Motherisk teratogen information service; Toronto's Hospital for Sick Children.

Sample: Forty-nine women (≤28 weeks gestation) callers to Motherisk taking a prescribed chronic medication not known to increase baseline malformation risk.

Research Procedures: Participants provided information for the Motherisk intake form then completed a self-report telephone survey before counselling and again two weeks later.

Main Outcome Measures: Change in medication usage and the effect of Motherisk counselling on Drug Therapy Self-Management.

Results: Motherisk counselling significantly (p<0.05) improved the knowledge domain but not perceived legitimacy or sense of empowerment. Motherisk counselling did not increase the probability that women would return to pre-pregnancy dosage levels.

Conclusions: Providing information does not directly affect medication-usage behaviour.
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>STATEMENT BY AUTHOR</strong></td>
<td>ii</td>
</tr>
<tr>
<td></td>
<td><strong>ABSTRACT</strong></td>
<td>iii</td>
</tr>
<tr>
<td></td>
<td><strong>ACKNOWLEDGEMENTS</strong></td>
<td>iv</td>
</tr>
<tr>
<td></td>
<td><strong>LIST OF TABLES</strong></td>
<td>vii</td>
</tr>
<tr>
<td></td>
<td><strong>LIST OF FIGURES</strong></td>
<td>ix</td>
</tr>
<tr>
<td></td>
<td><strong>LIST OF ABBREVIATIONS</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>SECTION 1</strong></td>
<td><strong>INTRODUCTION</strong></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>STATEMENT OF THE PROBLEM</strong></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>PURPOSE AND GOALS OF THE STUDY</strong></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><strong>RESEARCH QUESTIONS AND HYPOTHESES</strong></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td><strong>REVIEW OF THE LITERATURE</strong></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Medication self-management</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Measurement instruments</td>
<td>15</td>
</tr>
<tr>
<td><strong>SECTION 2</strong></td>
<td><strong>METHODS</strong></td>
<td>23</td>
</tr>
<tr>
<td></td>
<td><strong>RESEARCH DESIGN</strong></td>
<td>23</td>
</tr>
<tr>
<td></td>
<td><strong>INSTRUMENT DESIGN AND VALIDATION</strong></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Purpose and scope</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Preliminary item (question) generation</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Selecting and eliminating items (item reduction)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Formatting and delivery</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Frequency of question endorsement</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Survey instrument validation</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td><strong>EXPLORATORY STUDY</strong></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Selection of subjects</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Procedures</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Data collection</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Data analysis</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>ethics board approval</td>
<td>44</td>
</tr>
<tr>
<td><strong>SECTION 3</strong></td>
<td><strong>RESULTS</strong></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td><strong>PARTICIPATION RATE</strong></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td><strong>PARTICIPANT CHARACTERISTICS AT BASELINE</strong></td>
<td>47</td>
</tr>
<tr>
<td></td>
<td><strong>SURVEY INSTRUMENT VALIDATION</strong></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Frequency of endorsement</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Reliability testing</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Construct validity</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td><strong>EFFECT OF MOTHERISK COUNSELLING ON DTSM ATTITUDES</strong></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td><strong>EFFECT OF MOTHERISK COUNSELLING ON DECISIONS CONCERNING MEDICATION USAGE INTENTIONS</strong></td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Subgroup Exploratory Analysis</td>
<td>66</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1: Item (question) generation and reduction through revisions..............................................27

Table 2: Characteristics of the study group, a sample of the overall population of Motherisk callers and a subgroup of callers planning a pregnancy.................................................................47

Table 3: Study medications and medical conditions of study participants......................................50

Table 4: Frequency (percentage) of endorsement of each question in the study measurement instrument............................................51

Table 5: Calculation of the coefficient of variation for each domain as an estimate of reliability (N=49). ...52

Table 6: Values of Cronbach’s alpha for each domain of the study measurement instrument, pre-counselling and post-counselling....................................................................................52

Table 7: Reproducibility assessment by examining changes in the domain scores of the measurement instrument in participants with medication usage intentions remaining the same pre- and post-counselling (non-changers) (N=32)........................................................................................53

Table 8: Reproducibility assessment by calculating the within-person coefficient of variation in stable participants (non-changers) (N=32). ........................................................................................................53

Table 9: Responsiveness assessment by calculating the ratio of the difference in subjects who were unstable (changing) to the standard deviation of changes in stable (unchanging) subjects.................................................54

Table 10: Responsiveness assessment by examining changes in domain scores in participants with unstable responses (changers). (N=17).................................................................................................54

Table 11: Effect size for each domain and total score of the DTSM instrument as an estimate of responsiveness. (N=49) ..........................................................................................................................54

Table 12: Correlation between the pre-counselling total score for each domain and the change in total score post-counselling. ...........................................................................................................59

Table 13: Changes in domain scores, separately and combined, pre- and post-counselling. ..............60

Table 14: The Wilcoxon matched pairs signed rank test of scores for each domain and for the total score (N=49) ........................................................................................................................................60

Table 15: Callers with adverse effects upon stopping or reducing their dose of chronic medication and the association with increasing the dose again. (N=34) ........................................................................63

Table 16: Comparison of the effect of Motherisk counselling on women who are, and who are not, taking their medication as before pregnancy. (N=49) ........................................................................65

Table 17: Comparison of women who did, and did not, take their drug as prescribed pre-pregnancy. (N=49)65
Table 18: Comparison of the effect of Motherisk counselling on women who take their medication as prescribed/advised and those women who do not. (N=49) .................................................................66

Table 19: Association between type of medication (psychotropic vs. non-psychotropic) and the decision to stop the medication .................................................................67

Table 20: Association between presence of a psychiatric condition and the decision to stop the medication. 67

Table 21: Domain totals for subgroups taking or not-taking a psychiatric medications. ..........................68

Table 22: Summary of Results from the Satisfaction Survey (N=43) ...............................................................72
LIST OF FIGURES

Figure 1: A conceptual representation of the decision process of callers to Motherisk and methods of measuring the effectiveness of the service.................................................................4

Figure 2: Process of call handling by Motherisk during the study.................................................................6

Figure 3: A conceptual model of relationships between beliefs/attitudes and factors associated with drug therapy self-management.................................................................14

Figure 4: Study population sampling over the study period of 105 days.................................................................45

Figure 5: Participation flow diagramme........................................................................................................46

Figure 6: Total knowledge score (4 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).......................................................................................................................................58

Figure 7: Total perceived legitimacy score (4 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).......................................................................................................................................59

Figure 8: Total sense of empowerment score (3 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).......................................................................................................................................59

Figure 9: Changes in medication usage post-counselling according to pre-counselling medication use........61

Figure 10: Changes in medication usage intention decisions pre- versus post- pregnancy according to physician advice received........................................................................................................62

Figure 11 - Revised conceptual model of medication use decision process.................................................................84
LIST OF ABBREVIATIONS

CMU  Chronic Medication Users.
CMU-BR Chronic Medication User with Baseline Fetal Teratogenicity Risk.
CMU-BR-C Chronic Medication User with Baseline Fetal Teratogenicity Risk who gives consent to participate in the study.
CMU-IR Chronic Medication User with Increased Fetal Teratogenicity Risk.
DTSM Drug Therapy Self-Management.
EC Ethics Committee
prc Pre-counselling.
psc Post-counselling.
TIS Teratogen information service
SECTION 1 INTRODUCTION

STATEMENT OF THE PROBLEM

Since the thalidomide tragedy, the public has become increasingly concerned about the use of drugs in pregnancy. (Koren et al, 1990b) Evidence exists that pregnant women and their physicians overestimate the risks of taking a medication due to biased reporting by the media, lack of awareness of the underlying baseline risk, or societal biases. (Einarson et al, 1998) If this concern is great enough, pregnant women may consider terminating the pregnancy or stopping their medication. (Koren et al, 1990a) While stopping a recreational drug or a drug associated with fetal malformations may be beneficial, stopping a relatively safe drug being taken for therapeutic reasons, may not. In the case of women taking medication for a serious chronic medical condition, stopping the medication may result in reduced therapeutic benefits and even health deterioration of the mother or fetus. As an example, Einarson et al studied the consequences of abrupt discontinuation of antidepressants and benzodiazepines in 36 pregnant women. They found that medications were not tapered appropriately and suitable alternative therapy was not recommended, with resulting withdrawal symptoms and loss of control of the medical condition.

To help women and their doctors make informed decisions about medication use during pregnancy, valid information is essential. To meet this need, Motherisk was created with the following objectives: (Koren et al, 1993)

1. To provide authoritative information to assist pregnant women and their physicians in understanding the fetal risk associated with such an exposure during pregnancy.

2. To develop and maintain an active educational and research program in the area of reproductive and developmental toxicology at the undergraduate, graduate and postgraduate levels. The research program addresses unanswered questions on safety of drugs, chemicals and radiation during pregnancy and lactation.

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1 Motherisk is a program of the Hospital for Sick Children in Toronto. It is funded by the Ministry of Health.
Motherisk is a hospital-based teratogen information service (TIS) that provides risk-assessment information via the telephone to health professionals and to the general public. Incoming calls are received by information specialists, who decide whether the caller should be referred for a clinic appointment or to the physician on call or whether the query is such that the information specialist may answer the call satisfactorily. Of the approximately 1200 telephone queries received per month, 10-15% of callers are scheduled for a clinic appointment and counseled by a physician affiliated with Motherisk. Women may call on their own or their physician, another health professional or anyone else, can refer them.

Women callers to Motherisk are questioned about their current pregnancy, health problems, and use of medication. Counsellors then advise them whether the risk of birth defects to their fetus is increased above the baseline risk of 1-3% according to current medical research as outlined in standardized Motherisk statements (See Appendix 5). Some callers are asked to attend a clinic for further questioning and follow-up, based on the medication they are taking, their health status or their desire for a personal meeting. Callers use the information provided to make more informed decisions regarding medication usage, pregnancy termination, or the need for further assessment of their medical condition or treatment. (Koren et al, 1989; Koren et al, 1990b) Risk counselling as a therapeutic intervention can be considered a secondary preventive intervention in that risk-assessment information is given by Motherisk counsellors to pregnant women callers to prevent an unnecessary outcome (failure to achieve or maintain health goals for the mother or fetus) by modifying a risk factor (uncertainty of medication-risk). (Sackett et al, 1991) Providing information to patients rather than physicians in an attempt to effect changes in patients' personal health care decisions and beliefs is a non-traditional intervention.

Measuring the effects of a TIS, like any other professional service, is essential given the time and resources needed to maintain it. Traditional measures of effectiveness have included patient satisfaction with counselling (Ludowese et al, 1993), whether the counselling process was completed according to standardized procedures, and change in patients' perceptions of fetal risk to see if there is a reduction in the tendency to terminate the pregnancy. (Bolton et al, 1991; Immanaka et al. 1993; King, 1986) Patient satisfaction with care may have significant effects on
compliance and can be used as an effectiveness measure when medication compliance is the goal of a TIS. (Immanaka et al. 1993) Monitoring perceptions of fetal risk is a direct measure of whether the caller has understood and accepted the advice given. The tendency to terminate a pregnancy is such a complex decision that other confounding influences make it difficult to directly link risk-counselling and pregnancy terminations. The outcome of pregnancy is not a valid effectiveness measure because other medical interventions over the course of the pregnancy would have influenced the results as well. (Pearson, 1982) Examining the success of disease management is also inappropriate because treatment is never 100% successful and medical conditions fluctuate in severity regardless of treatment. Therefore, the purpose of this study was to identify and then measure an alternative outcome to assess the effectiveness of a TIS. Possible outcomes considered for the study included the effects of counselling on patient compliance, on patients' intentions to use a prescribed drug or on patients' beliefs/attitudes concerning drug usage in pregnancy. A conceptual schematic representation of the decision process mothers might follow when calling the TIS is presented in Figure 1. Also included are the traditional and potential ways of measuring TIS effectiveness. Results of the study might be used to develop a decision aid to help Motherisk callers make the decision to take or not to take a medication during pregnancy or the results might suggest ways to improve Motherisk's counselling methods. Results could also be used to identify outcomes for use in other types of studies such as economic evaluations.
Figure 1: A conceptual representation of the decision process of callers to Motherisk and methods of measuring the effectiveness of the service.

- Prescriber advice
- Callers to teratogenic information service
- Increased teratogenic risk
- Baseline teratogenic risk
- Decision to terminate pregnancy
- Decision to continue pregnancy
- Decision to stop prescription medication use
- Decision to continue prescription medication use
- Maintain dosage level
- Change dosage level
- Outcome

Effectiveness Assessment Method:
- Previous Process Evaluation
  - Client satisfaction
- Previous (Intermediate) Outcome Evaluation
  - Change in perception of fetal risk
- Proposed (Intermediate) Outcome Evaluation
  - Change in intention to terminate pregnancy
  - Drug usage intention, beliefs about medication usage in pregnancy and factors affecting those beliefs

Effectiveness Assessment Method:
- Client satisfaction
- Change in perception of fetal risk
- Change in intention to terminate pregnancy
- Drug usage intention, beliefs about medication usage in pregnancy and factors affecting those beliefs
PURPOSE AND GOALS OF THE STUDY

The purpose of this study was to investigate the effects of risk counselling by Motherisk on medication usage intentions and selected factors hypothesized to influence attitudes towards medication usage intentions, of pregnant women callers. To gather the required information, a survey instrument was designed specifically for this study.

Study results were used to partially validate the survey instrument, in this setting. The process of call handling by Motherisk during the study is presented in Figure 2.

The goals of the study were:

1. To describe the sub-population of chronic prescription medication users (CMU – Figure 2 -Box 2c) who contact the Motherisk clinic seeking information about risk to the fetus from exposure to a prescription medication needed for a chronic medical condition.¹

2. To describe the sub-population of chronic prescription medication users who contact the Motherisk clinic seeking information about fetal risk from exposure to a prescription medication that was considered by Motherisk to not increase fetal risk above the baseline. (CMU-BR-Figure 2- Box 2f)

3. To describe the factors influencing medication usage intentions and the medication usage decisions made by the sub-population of Motherisk clients defined in 2 above, who consent to participate in the study. (CMU-BR-C - Figure 2 - Box 2i)

4. To determine the nature and extent of the effect, if any, of the Motherisk service on factors influencing medication usage intentions and medication usage decisions in the sub-population of Motherisk clients defined in 3 above. (CMU-BR-Figure 2- Box 2i)

5. To determine callers' satisfaction with the Motherisk service.

¹ Defined as a condition requiring the use of a medication for the remainder of the first trimester or for at least two more weeks, whichever is greater.
Figure 2: Process of call handling by Motherisk during the study.
RESEARCH QUESTIONS AND HYPOTHESES

1.1 What proportion of the total client population (Figure 2- Box 1) that makes initial contact with the Motherisk clinic in a designated period has a medical condition for which medication has been prescribed and is expected to be required for the duration of the pregnancy? (Chronic Medication Users (CMU) – Figure 2- Box 2c)

1.2 In what proportion of this sub-population of CMUs, is the prescription medication not considered, according to Motherisk evidence-based statements, to increase the risk of fetal malformations above a baseline of 1-3%? (Figure 2- Box 2f)

1.3 What are the self-reported characteristics (age, referrer, gestational history, gestational age, malformations in previous pregnancies, medical history, current medical problems, prescribed drug therapies including name, date of start and stop, dose, route, and frequency, use of recreational drugs) of the total client population (Figure 2- Box 1) and of the CMU sub-population (Figure 2 - Box 2c)?

2.1 What are the self-reported demographic characteristics (as described above), medical problems, and prescribed drug therapies of the sub-population taking chronic medication with a baseline risk of malformations (CMU-BR - Figure 2 – Box 2f)?

3.1 Compared to the pre-counselling level, what proportion of study participants at the post-counselling interview (CMU-BR-Cs – Figure 2- Box 2m ) report that they are continuing to use their prescription medication?

The null hypothesis is

\[ H_0: \ p_{pre} = p_{pos} \]

And the alternative hypothesis is

\[ H_1: \ p_{pre} < p_{pos} \]

where \( p_{pre} \) is the proportion of study participants taking their medication pre-counselling and \( p_{pos} \) is the proportion of study participants taking their medication post-counselling.

3.2 How do the subgroups of CMU-BR-C (Figure 2 – Box 2i) using medication at the same, higher or lower dosage level, differ in respect to self-reported demographic characteristics, medical problems, prescribed drug therapies and documented clinic attendance?

3.3 What factors are associated with an increase in medication usage, relative to pre-pregnancy levels, following Motherisk counselling?
4.1 For all study participants (CMU-BR-C), what changes from baseline, if any, have occurred at follow-up in clients' medication-related knowledge, perceived legitimacy of their drug therapy, and sense of empowerment as managers of their drug therapy?

The null hypothesis is

\[ H_0: \bar{X}_{prc} = \bar{X}_{psc} \]

And the alternative hypothesis is

\[ H_1: \bar{X}_{prc} < \bar{X}_{psc} \]

where \( \bar{X}_{prc} \) is the measurement instrument score mean pre-counselling and \( \bar{X}_{psc} \) is the measurement instrument score mean post-counselling; i.e., the research hypotheses are that Motherisk counselling will,

1) result in callers taking their medication as they had done before finding out that they were pregnant, and

2) improve callers' knowledge about the risk of their medication in causing fetal malformation, improve their perception of the legitimacy of taking their medication during pregnancy and improve their sense of empowerment concerning drug medication use during pregnancy.

The ability of patients to successfully manage the way they take medication is affected by internal factors (e.g. personal beliefs such as perceived legitimacy of drug therapy, sense of empowerment over their drug management) and external factors (e.g., knowledge, the ability to pay). Ultimately patients choose, consciously or subconsciously, whether and at what dose and dose-frequency, to take a drug to achieve results. Drugs are not always taken as prescribed. During pregnancy, non-compliant under-dosers may increase medication use to obtain better control of a medical condition for the benefit of the fetus. Alternatively, women may decrease medication-use to lower the medication-related risk to the fetus. The goal of Motherisk counselling is to effect a change in the caller either by increasing her knowledge or by putting the actual risk associated with taking a medication in pregnancy in perspective by comparing any added risk to the baseline risk (1 to 3%) of fetal malformations. Counselling may improve the ability of women to make well-informed medication decisions by affecting their personal beliefs or external factors.

5.1 How satisfied are study participants with the Motherisk service?
REVIEW OF THE LITERATURE

The literature review will be presented in two parts: medication self-management and the development of measurement instruments.

MEDICATION SELF-MANAGEMENT

It can be hypothesized that risk counselling provided by Motherisk may affect callers' medication compliance or usage or their knowledge, attitudes and beliefs that contribute to medication usage decisions. A literature search on the potential effects of patient drug counselling, in the University of Toronto journal database, and Medline¹ and IPA¹ from 1966 to 1998, produced reports primarily addressing the effect of drug information on drug compliance. (Rosenstock, 1985; Blackwell, 1973; Pullar, 1991; Conrad, 1987) However, upon reviewing the literature, drug compliance did not seem to be an appropriate outcome for evaluating the success of Motherisk counselling for the following reasons. Studies have shown that knowledge predisposes patients to successful drug-taking behavior but rarely improves compliance on its own. (Sackett, 1991; Qing et al, 1992; (Barnhoorn et al, 1992; Wagner, 1996) Additionally, when used as an outcome in studies, compliance is difficult to measure; patient interviews and tablet counts are often misleading or inaccurate. (Sackett et al, 1991) An acceptable compliance level is also difficult to define. (Pullar, 1992) A focus on compliance also assumes that patients are passive recipients of physicians' prescriptions and that taking medications exactly as prescribed leads to the best outcome. (Playle et al, 1998) Van Trigt et al (1994) warn that counselling pregnant women about the drugs they are taking may actually lead to “reasoned noncompliance”. Therefore, drug compliance, which implies use-as-directed, is probably not be the best measure of the effect of Motherisk. (Conrad P, 1985) Motherisk counselling probably affects another more complex behaviour related to compliance.

The argument can be made that MR callers are primarily seeking information as a basis for making a drug usage decision in pregnancy. Pregnant women callers have concerns for both their

¹ Search terms included: counselling, genetic counselling, information services, patient compliance, patient education, patient satisfaction, questionnaires, self-assessment, self-care, self-efficacy, self-concept, teratogens
own and their fetus' well-being particularly when the risks and benefits of therapy are, to them, unclear or contradictory. (O'Connor et al, 1994) But for every woman, the decision context is different depending on her environment, personality, history and demographics. Although decision-making is difficult to measure directly, the process and outcomes can be measured. (Bekker et al, 1999) The process can be measured by asking callers directly how the Motherisk information was used or how it was useful. The outcomes that can be measured include health behaviours or decisions, knowledge achieved, changes in values/attitude/beliefs, efficacy, and personal affect (e.g., anxiety, regret, satisfaction etc.). (Bekker et al, 1999) While some outcomes such as level of knowledge about health and illness have not been shown to accurately predict what decision will be made, they do contribute to the decision-making behaviors. (Rosenstock, 1985)

Before designing a study to assess the medication use decision-making process inherent before, during and after Motherisk counselling, it is helpful to explore the possible relationships between values/beliefs/attitudes, knowledge and drug usage decisions. To this end it is advantageous to identify concepts and supporting theories that might help define and characterize these relationships. These concepts/theories can then be used to identify relevant outcomes from risk counselling, to identify domains to include in a measurement instrument and to suggest the most useful questions to ask in a qualitative interview. Drug therapy self management (DTSM) is one such concept that was found to be relevant and which is partially grounded in two theories; Bandura's Social Cognitive (learning) Theory (SCT) and the Health Belief Model (HBM). (Rosenstock et al, 1988)

Drug therapy self-management (DTSM) (Marshman, 1997) shares properties with two similar ideas reported in the literature, "behavioural self-management" (McCann et al, 1990), "self-regulation" (Conrad, 1985; Conrad, 1987) Behaviours of Motherisk callers that correspond with DTSM include the way they actively participate as agents in their health care, show interest and initiative in their medication usage decisions in pregnancy, and seek out information or advice from health professionals, then alternatively accept or challenge that advice. Callers may even make recommendations of their own Therefore, concepts relating to DTSM can be used to help identify specific outcomes from the decision-making process and more importantly, how they inter-relate.
The SCT holds that expectancies and incentives determine behavior. In this case, the main cognitive factors driving health-related actions are

- outcome expectations (incentives such as changes in health status, peer/family approval, economic gain)
- expectations about how individual behaviours or environmental situations influence outcomes
- expectations about one's ability or competence to perform the behavior (self-efficacy).
  (Imanaka et al, 1993; Rosenstock et al, 1988)

The HBM proposes that the major components predicting the likelihood of health-related actions are

- perceived threats to health (the belief that one is susceptible to serious health problem/perceived threat)
- perceived benefits of behavior
- perceived costs or barriers involved that must be overcome. (Imanaka et al, 1993; Rosenstock et al, 1988)

To summarize, the basis of DTSM is the patient's belief that she can contribute to, and assert some control over her own drug therapy. DTSM contains elements of goal setting and self-monitoring, usually in accordance with changing life situations. (Conrad 1987; Conrad 1985). The major components contributing to DTSM are beliefs and factors affecting those beliefs. Beliefs in the context of DTSM include a sense of empowerment, perceived legitimacy of drug treatment, and self-efficacy. These beliefs will now be examined more closely.

Feelings of legitimacy of treatment come from a patient's understanding of her illness and its consequences, her views on health or what threatens her health, her understanding of the need for treatment, the benefits or consequences of treatment and her risk-benefit analysis. (Imanaka et al, 1993; Redland et al, 1993) Patients also determine if there is an acceptable balance of efficacy
and tolerability: costs and barriers. (Conrad, 1987; Imanaka et al, 1993) Legitimacy of drug treatment from the patient's viewpoint is important because without it patients can become complacent and forgetful. (Blackwell, 1973) A sense of legitimacy arises from personal expectations from past experiences. (Conrad, 1987; Rosenstock, 1985)

Empowerment concerns the belief in a personal authority to make, and take responsibility for decisions regarding drug therapy. The patient may or may not see herself as having an important role in deciding how or when to take medication. She may or may not feel free to make her own decisions. These feelings may be based on whether or not she feels as if she is an active participant in her own health care. Empowerment may be evidenced by patients engaging in "testing" behaviour i.e., stopping drug to see what happens, reducing dose to see if there is still a benefit, and stopping the drug if an expected outcome is not achieved. (Conrad, 1987)

Drug therapy self-efficacy concerns belief in one's ability to make decisions about drug-taking behavior or belief in one's ability to take control of drug-taking behaviour. It is an expectation that one can execute a behavior required to produce a desired outcome. Accordingly, an increase in self-efficacy may be the common medium by which drug therapy self-management is improved, key behaviors are changed and illness outcomes are affected. (Redland et al, 1993; De Geest, 1994)

In addition to the beliefs suggested by the SCT and HBM, the factors affecting those beliefs are also important. These include: the living environment, personal attributes, medication-related functional ability (e.g., ability to open a medication bottle), and knowledge of health and illness. At least one author describes these factors as being alternately reinforcing, predisposing or enabling regarding their effects on health beliefs. (Barnhoom et al, 1992) Other factors create a barrier/obstacle or alternatively have a supporting/facilitator role in DTSM while not directly influencing health beliefs. (Barnhoom et al, 1992; Redland et al 1993) Others have an indirect effect on health beliefs and may affect or determine patient responses to reinforcing, enabling or predisposing factors. (Barnhoom et al, 1992) While beliefs about drug therapy may accurately predict whether or not a person will comply with medication therapy, factors affecting beliefs, in and
of themselves, do not. (Rosenstock, 1985) Rather, they modify or modulate drug usage
behaviours, affecting the extent to which they are exhibited. (Blackwell, 1973; Redland et al, 1993)

Environmental factors have been subdivided into groups according to the role they play in
affecting beliefs. For example, medication aids, schedules and personal routines play a supportive
role. Supervision and encouragement are reinforcing. Social support and financial assistance can
be described as enabling. Distractions, high drug costs, adverse side effects and multiple drug
prescriptions can create barriers. (Barnhoorn, 1992) Personal attributes such as demographics,
socioeconomic factors, education, drug-therapy functional ability, and values can also indirectly
affect patient beliefs and behaviours. So can the disease condition itself.

The provision of knowledge in an attempt to reduce decisional uncertainty, is a major
determinant of perceived legitimacy of drug use during pregnancy. Knowledge has scope,
accuracy, status and reliability; its effectiveness depends on these qualities and how it is interpreted
or understood. Knowledge about a medication's likelihood of causing fetal malformations gives
Motherisk callers a more realistic expectation of the risks involved. Callers can be expected to
interpret risk information based on its presentation (counsellor's attitude, authoritativness, skill),
their relationship with the provider and the degree of confidence they have in the information.
(Leclercq, 1995; McCann et al, 1997)

A conceptual model of outcomes and influential factors in the DTSM process and how they
inter-relate is provided in Figure 3.
**Figure 3:** A conceptual model of relationships between beliefs/attitudes and factors associated with drug therapy self-management.

<table>
<thead>
<tr>
<th>Information Used to Form or Influence Beliefs/Attitudes:</th>
<th>Knowledge &amp; Information</th>
<th>Drug-therapy functional ability</th>
<th>Environmental Factors Affecting Beliefs (Beliefs Are Environment-Dependent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERSONAL FACTORS AFFECTING BELIEFS (Personal Attributes, Values, Demographics*)</td>
<td></td>
<td></td>
<td>- need a supportive environment (family, friends) (Johnson, 1996)</td>
</tr>
<tr>
<td>TYPE OF INFORMATION USED TO FORM OR INFLUENCE BELIEFS/ATTITUDES:</td>
<td>- personal experiences</td>
<td>- cause/effect relationships</td>
<td>- performance accomplishments</td>
</tr>
<tr>
<td></td>
<td>- consequences of actions (incentives)</td>
<td>- expected outcomes (incentives)</td>
<td>- vicarious experiences</td>
</tr>
<tr>
<td></td>
<td>- value of outcomes</td>
<td></td>
<td>- verbal persuasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- physiological state</td>
</tr>
<tr>
<td>BEHAVIOUR:</td>
<td></td>
<td></td>
<td>INTENT TO ADHERE TO A DRUG REGIMEN (as a process measure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DRUG ADHERENCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effective Drug Therapy Self-Management</td>
</tr>
<tr>
<td>OUTCOMES:</td>
<td>Economic Benefits</td>
<td>Improved health status</td>
<td>Improved quality of life</td>
</tr>
</tbody>
</table>

*Note: Personal Attributes, Values, Demographics include personal characteristics such as age, gender, socioeconomic status, and cultural background. These factors can influence beliefs and attitudes towards drug therapy, and ultimately affect drug adherence.*
The conceptual model of DTSM is useful in identifying outcomes and influential factors that may be modified by Motherisk counselling. Study outcomes can be described in terms of the following types of variables: cognitive (thoughts, beliefs, attitudes, expectations, reasoning etc.); affective (emotions, feelings etc.); behavioural (doing, compliance/adherence); or interpersonal (stressors, social supports etc.). (Dolinsky, 1996) Cognitive variables such as beliefs and attitudes, when compared to other types, are more assessable to measurement by telephone, an important consideration for a study involving Motherisk callers.

MEASUREMENT INSTRUMENTS

The background literature on measurement instruments as it relates to this study will be presented under the following headings: characteristics of measurement instruments and the development and testing of measurement instruments.

Characteristics of measurement instruments

Because the beliefs/attitudes associated with DTSM are subjective, self-reporting is essential. (Streiner et al, 1995) In addition, previous studies have shown that self-report measures of the related concept of compliance correlate highly with other types of measures. (Conrad et al, 1987; Imanaka et al, 1993) Therefore, self-reporting can be justified as an appropriate method of measurement for the purposes of this study. Unfortunately, there are limitations to self-reports. (Barker et al, 1994).

- They are subjective.
- They are not always truthful.
- There are limits to a person's conscious self-knowledge.
- People don't always know what influences their behaviour.
- People can be self-serving.
- People have biases in accounting for their own behaviour versus others' behaviour.
To obtain a more comprehensive understanding of the effects of counselling both quantitative (measurement instrument) and qualitative (interviews, directed questions) self-reporting can be used in a complementary fashion. In essence, the same question is approached from two different angles in a questionnaire that can be thought of as a survey instrument.

A quantitative instrument is useful for measuring how much of an attribute is present and is a good choice for measuring knowledge, perceived legitimacy, sense of empowerment and service satisfaction. For these “domains”, a questionnaire is superior to unaided personal judgement because it can be more objective, more easily communicated, and more economical to collect in terms of time and money. The information obtained can be summarized easily, reported in finer detail, analyzed statistically and assessed for reliability and validity. (Nunnally, 1978) Quantitative data also increases the credibility of qualitative data. (Jayawickramarajah, 1992)

For the measurement instrument, each chosen domain/attribute has one or more dimensions and each dimension should be represented by at least one question for several reasons: 1) individual items usually have only a low correlation with the attribute being measured, 2) increasing the number of items increases the ability to make finer distinctions and 3) individual items have considerable measurement error and are unreliable on their own whereas measurement error averages out when numerous items are summed. (Nunnally, 1978) Instruments are normally tested to determine the proportion of respondents that endorse each question. Only questions endorsed by 20-80% of respondents are normally used. (Streiner et al, 1995)

Including a qualitative component in the study is useful to obtain unquantifiable data and to interpret quantitative results. Qualitative methods such as case study reviews are considered legitimate approaches to evaluating and gaining new insights into educational programs. (Jayawickramarajah, 1992) Other advantages of qualitative methods are as follows: (Barker et al, 1994)

- Individuals can be studied in more detail.
- More complex aspects of the experience can be elucidated.
Generating hypotheses from a qualitative interview is easier.

Participants are allowed to express themselves making their experience more enjoyable or satisfying.

To collect data, three options exist when selecting the best instrument, questionnaire or technique; use an existing one, modify an existing one, or develop a new one. A new instrument should be able to explain a broader range of findings, and make more accurate predictions about a person's behaviour than methods currently available. (Streiner, 1995) When possible, at least some parts of a new instrument should have its roots in a survey instrument that already has validity and reliability. (Redland et al, 1993)

For research intending to evaluate the outcome of a clinical service, the emphasis of the instrument should be evaluative rather than discriminative or predictive. This means that it should have the ability to detect individual differences. (Redland et al, 1993) If the patient changes, the measure changes. In other words, it should be highly responsive. (Spilker, 1996)

A specific rather than a generic instrument would be expected to be more responsive to change in very specific study populations. (Spilker 1996; De Geest 1994) In addition, a specific instrument lends itself to more appropriate and relevant questions and keeps the survey instrument shorter. The limitations of this approach are that results cannot be compared across conditions, the questionnaire can only be used for the population or intervention for which it was developed and there are fewer relevant domains that can be used. (Spilker, 1996) Additionally, participants recruited for survey instrument development must be clearly defined by precise inclusion/exclusion criteria.

Development and Testing of Measurement Instruments

Literature relating to the steps in development and testing of the draft survey instrument is discussed below.

New instruments for measurement of the outcomes of health services are developed through a series of steps as follows (Barker et al, 1994):
1. Develop a draft instrument.

2. Pilot the instrument on colleagues, friends, support staff to pretest questions, correct phrasings, clarify meanings, shorten etc. For some types of instruments or scales up to 100 patients might be recruited to help in refining questions. (Spilker, 1996)

3. Pilot the instrument using a sample of 20-30 respondents to enable informal reliability and validity testing and factor analysis to see which items should be dropped or added before doing a larger, formal study.

4. Perform a formal reliability study using a large sample (over 120 participants) to examine item characteristics, internal consistency, factor structure, reliability, and validity.

Scoring/scaling options
Attitudes and opinions lie on a continuum; therefore scaling options are limited. The literature indicates that dichotomous scales increase error, uncertainty, and confusion, and decrease reliability and efficiency. The net result is a loss of information that would have been easy to collect. Visual analogue scales are potentially difficult to describe over the phone and for the patients to understand. (Streiner et al, 1995) Alternatively, adjectival scales are easier to understand and allow for discrete responses. Likert scales let participants express an opinion by rating their agreement with a statement. This method reduces confusion over the phone because the response choices are the same for each question. (Streiner et al, 1995) Because respondents tend to avoid extremes (end aversion bias) at least five points are usually needed for reliability. (Barker et al, 1994). Using an odd number allows participants to express no opinion or a neutral one rather than forcing them to take sides.

Formatting & instrument delivery
The benefits of telephone instruments according to the literature are that callers can remain relatively anonymous, items are not as easily omitted, open-ended questions can be asked, the interviewer can determine if the participant is having language or comprehension problems, and respondents can ask their own questions. The bias caused by appearance is eliminated and evidence shows that people tend to report more health-related events over the telephone rather
than in person. (Streiner et al, 1995; Conrad et al, 1994) The limitations of telephone delivery are that participants may have difficulty choosing options or answering complex questions with several parts. In addition, participants may be difficult to call back.

**Instrument testing and reliability**

Measurement instruments should be tested for reliability and validity.

Reliability refers to the degree of reproducibility of a measurement or whether repeated observations obtain the same result. Reliability is assessed according to the type of instrument and the type of consistency needed. (Barker et al, 1994) For reliability statistics, "ordinal scales can be analysed as if they were interval scales." (Barker et al, 1994)

Test-retest reliability is important when a change in score is used as evidence of an effect. If change in score occurs over time regardless of any intervention, the survey instrument would be unstable and unreliable for study purposes. If the time between repeated measurements is too short the result may reflect memory; if the time between measurements is too long there may be problems with internal validity because of behavioural maturation that occurs over time. The test may also be reactive in that the questions themselves may change respondents' attitudes once they have reflected on them over the time between the first and second test. (Nelson, 1980)

Symptom scores are compared using the Spearman rank correlation. (Streiner et al, 1995) While the stability must be >0.5, the optimal reliability is between 0.6 and 0.9. A stability above 0.9 means that some items may be trivial or that there are too many items or too much inter-correlation. (Nunnally, 1978; Tedesco et al, 1991)

The most widely used test of internal reliability or homogeneity of a measure is the internal consistency or alpha coefficient (Cronbach’s alpha). (Cronbach, 1951) It is based on the average correlation among all items measuring a particular construct. The higher the correlation of the items within the scale, the higher is the correlation with the factor they measure. Optimally the correlation should be between 0.7 and 0.9. (Streiner et al, 1995) Cronbach’s alpha is more suited to scales with several parallel items. Additionally, items within an evaluative survey instrument do not need to correlate with each other but need to show that they change consistently over time.
Therefore this test is not as useful for evaluative scales containing a limited number of questions in each domain. (Kirshner et al, 1985) Inter-rater reliability is mainly used for instruments that rely on observation; so it is not appropriate for this survey instrument that relies on self-report. (Barker et al, 1994)

Reliability may also be determined using the coefficient of variation defined as the standard deviation divided by the mean multiplied by 100 (%). This measures the compactness or relative dispersion of the data, so it is not a sufficient measure of reliability on its own. A result less than one indicates compact data. A result more than one indicates that there may be large within- or between-patient differences or a large measurement error or a combination. (Bellamy, 1993)

**Instrument responsiveness and reproducibility**

Responsiveness, defined as the sensitivity to change of an assessment technique, can be described using the effect size, a descriptive statistic promoted by Cohen. (Bellamy, 1993; Cohen, 1977) The effect size relates the magnitude of the change score to the variability of the measure and is calculated by dividing the mean change score by the standard deviation of the measure. In comparative studies, small, medium and large effect sizes have values of 0.2, 0.5 and 0.8, respectively. (Bellamy, 1993)

Responsiveness and reproducibility can also be assessed by dividing patients into two groups. The first group includes patients who changed between two measurement events; the second group includes patients who did not change. The data from changers (unstable) is used to assess responsiveness. The data from non-changers (stable) is used to estimate reproducibility. (Spilker, 1996) Reproducibility means that an assessment technique will give similar results in an individual over two or more points in time if the attribute measured in that individual has not changed. (Streiner, 1995) Reproducibility has two components, systematic changes in scores over time and variability occurring in those changes. (Guyatt et al, 1989). Reproducibility can be assessed by examining changes in domain scores of a measurement instrument in stable patients. Non-significant changes indicate that there was no systematic change in scores over time. The variability in scores in stable subjects can be assessed by calculating a within-patient coefficient of
variation for each domain. The lower the score the more reproducible the results for individual patients. (Streiner et al, 1995)

**Instrument validity**

Validity is the degree to which a survey instrument measures the attribute(s) it is supposed to measure under the conditions of use. The different types include: content (face, relevance, coverage), criterion, and construct validity. (Streiner et al, 1995)

Specifically, content validity is a subjective appraisal of whether the items of an instrument adequately represent the domain they are supposed to measure according to clinical experience and literature reviews. The list of questions must be comprehensive in measuring the scope of each attribute in all its dimensions. Ultimately however, content validity depends on the judgement of, and agreement among, experts that the survey instrument measures what is should. (Streiner et al, 1995; Nunnally, 1978; Bellamy, 1993)

Criterion-related validity attempts to correlate the score from the new survey instrument with a validated scale from the literature or a "gold standard". If the two scales have a correlation coefficient of 0.4-0.8, then the same attributes are considered to have been measured. (Streiner et al, 1995)

Construct validity refers to how well an instrument measures the theoretical construct that it should measure. Testing of construct validity may not be needed in small-scale experiments testing a new intervention or requiring a newly developed outcome measure if the intention is to show group differences: measures of content validity may suffice. (Nunnally, 1978) If a measure is to be assessed for convergent and discriminant construct validity testing, predictions for hypothesis testing are prepared a priori. The rationale for each statement is based on expectations arising from the hypothetical model. The correlation coefficient is calculated between the results obtained with the new instrument and some aspect of the condition/patient or the patient's behaviour. Correlations are classified as follows: closely related, $r \geq 0.5$, moderately related, $r \geq 0.4$, and some relation, $r \geq 0.3$. (Streiner et al, 1995; Spilker, 1996; Nunnally, 1978)
Convergent construct validity is tested by comparing results of questions that should be in agreement according to the construct. Different measures of the same construct should be highly correlated. Discriminant/divergent construct validity is tested by comparing the results of questions that should not correlate according to the construct and addresses whether items correlate more with the construct they are intended to measure rather than with other constructs. Because scores from self-report survey instruments are often moderately inter-correlated, data from a qualitative interview should be used to interpret the construct test data from an alternative viewpoint.

(Nunnally, 1978)
SECTION 2 METHODS

RESEARCH DESIGN

The study reported herein was an observational study with a one-group pretest-posttest design considered quasi- or non-experimental because measurements were taken without changing the pre-existed Motherisk counselling intervention. The pre-test/post-test, paired comparison design was used to control for variability among subjects by having each subject act as her own control. (Daniel, 1995) The results focused on the individual without reference to or comparison to others. This design allowed a direct estimate of change in individuals over time in an effort to examine associations, in contrast with experimental designs that are more concerned with cause and effect. (Barker et al, 1994) Therefore, the study plan was to ask enrolled Motherisk callers to complete a pre-counselling survey, give them the standard Motherisk counselling, then obtain a follow-up post-counselling survey 7 to 14 days later.

The focus of this prospective, longitudinal, exploratory and descriptive study, was a selected sub-population of callers to Motherisk who contacted the service during a specified period of time. The study subgroup (CMU) was defined schematically in Figure 2 - Box 2c and represents pregnant women with a chronic medical condition for which they are taking a prescription medication that will be needed for the remainder of the first trimester or for at least two weeks more, whichever is greater. Of particular interest was that subgroup (CMU-BR, Figure 2 – Box 2f) taking medication that did not increase the baseline fetal teratogenicity risk according to the evidence-based documentation compiled by Motherisk.

The study also examined the documentary data for a sample of all callers to Motherisk over the duration of the study represented in Figure 2 - Box 1 and collected selected data, prospectively, for callers in Exhibit B, Box 2i.

The planned duration of data collection was 2.5 months.
INSTRUMENT DESIGN AND VALIDATION

PURPOSE AND SCOPE

A literature search failed to uncover an appropriate, validated survey instrument that could be used in this study to measure the effect of Motherisk counselling on pregnant women's attitudes towards managing their drug therapy. (Streiner, 1995) Therefore, as part of the study, a survey instrument was developed. To increase comprehensiveness, a quantitative component (measurement instrument) and a qualitative component (open-ended questions) were included in an attempt to capture several aspects of DTSM that might be affected by Motherisk counselling. (Streiner et al, 1995)

Qualitative methods were considered more appropriate for collecting information on drug usage decisions, the way risk information was used in decision-making, previous advice from other health professionals, demographic information and personal medical history. An open-ended question about previous advice received about medication risk during pregnancy was included to gauge whether the patient's doctor had changed the prescription or whether there was conflicting or supportive advice given. According to Einarson et al (1998), patients receive advice from family members, friends and health professionals throughout pregnancy and this advice might affect how receptive they are to Motherisk information. The health behaviour/decision was measured by using, as a proxy, the caller's stated intention to change or maintain the current medication-taking schedule.

The quantitative component (measurement instrument) was designed to meet the following criteria (Guyatt et al, 1989):

- items reflected outcomes/attributes that were hypothesized to be influenced by Motherisk counselling
- summary scores on each domain were to be evaluable statistically
- questions were to be short, unambiguous and simple to administer over the telephone
items were to be understandable to someone with an average literacy level

- the instrument was to be valid

Following discussion with Motherisk counsellors and after reviewing the DTSM literature, the beliefs/attitudes hypothesized to be most likely influenced by counselling and yet still measurable during a telephone interview included the perceived legitimacy of taking a drug in pregnancy and the sense of empowerment concerning drug usage decisions. Knowledge as an outcome was included even though attaining knowledge doesn't mean that information is actually used.

The degree of satisfaction with the Motherisk service was included to help interpret the results of the survey instrument and interview and to give consumers an opportunity to give their opinions about this health service. All participants were given the satisfaction survey following the post-test. The satisfaction survey had a non-randomized design. This descriptive, one-group design is commonly used for consumer satisfaction studies. Participants were asked open-ended questions to help draw out any comments, ideas or attitudes they had about their counselling experience that the survey instrument might not have covered. The depth of this portion of the interview was not pre-determined. The results were used to help interpret the results of the survey instrument.

The survey instrument was designed to gather information from the patient's perspective through self-report because cognitive variables are not directly observable even if callers could be observed during telephone counselling sessions. Because the instrument used was not previously validated, the instrument was piloted within this exploratory study, i.e., the same group that was used to validate the instrument was also used to explore the effectiveness of Motherisk counselling.

It was anticipated that study results would suggest ways to improve counselling methods. Alternatively, if Motherisk decided to alter their counselling process, the instrument could be used to compare results with those of the original process and measure the effects of those changes.
PRELIMINARY ITEM (QUESTION) GENERATION

The theoretical base for questions used in the instrument was the Social Cognitive (learning) Theory (SCT) and the Health Belief Model (HBM). Concepts from these two theories have been combined as reported by Rosenstock (1985) in a study involving diabetics and their treatment-related behaviours. Potential topics and wordings for questions were gleaned from:

- review studies in related areas of research e.g., drug compliance, self-efficacy, teratogen information services, behavioral medicine, patient education and counselling
- other survey instruments developed for DTSM (Marshman, 1997)
- other survey instruments developed for related areas of research with a counselling component (De Geest et al, 1994; Dilorio et al; Price et al, 1994; Guyatt et al, 1989; Lorig et al, 1989; Lev et al, 1997; VanDrel et al, 1997; Anderson et al, 1995)
- characteristics of callers that might differentiate them during different time points
- experts/clinicians
- Motherisk counsellors
- Ethics Committee members (Hospital for Sick Children, Toronto, Canada)
- Women with children

In addition, six Motherisk callers attending the Motherisk clinic were asked to participate in a structured qualitative interview to capture their thoughts and concerns surrounding medication use in pregnancy. A summary of their responses can be found in Appendix 2.

Each quantitative question was placed in the proper domain; then every question was examined for bias in eliciting a response. Finally, questions were grouped empirically.
SELECTING AND ELIMINATING ITEMS (ITEM REDUCTION)

Following the development of an original set of questions, a series of revised survey instruments with changing domains and attributes (see Table 1) were developed over time with the assistance of:

- The Motherisk staff (director, associate director, assistant director, manager, two counsellors)
- Members attending the Clinical Epidemiology Rounds on May 26, 1998 (acting as the Scientific Review Committee for the Ethics Committee)
- The Social and Administrative Pharmacy Group (Faculty of Pharmacy, University of Toronto)
- The graduate Program Advisory Committee
- Members of the public at large (a woman in the first trimester of pregnancy)
- A Graduate student in Sociology
- The Hospital for Sick Children's Ethics Committee and liaison (Ph.D. in Pharmacology)

Table 1: Item (question) generation and reduction through revisions.

<table>
<thead>
<tr>
<th>Knowledge/Cognitive appraisal</th>
<th>Number of questions in each attribute category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Perceived probability of malformations</td>
<td>3</td>
</tr>
<tr>
<td>Amount of knowledge</td>
<td>1</td>
</tr>
<tr>
<td>Confidence in knowledge</td>
<td>1</td>
</tr>
<tr>
<td>Certainty of knowledge</td>
<td>6</td>
</tr>
<tr>
<td>Perceived legitimacy of medication</td>
<td>4</td>
</tr>
</tbody>
</table>
Each question was placed in the most appropriate domain e.g., knowledge. An effort was made to ensure that the number of questions in each domain reflected its importance but this decision was made empirically. Questions/items were excluded if they were perceived to be irrelevant, unimportant, or unlikely to change following Motherisk counselling. Alternatively, questions were revised if they were confusing or biased. The survey instrument was then administered to two callers to adjust question wording to facilitate understanding.
Normally, the next step in item reduction would have been to pre-test the survey instrument with at least five Motherisk callers to assess their understanding of each question. However, the Ethics Committee did not want actual callers to be questioned so closely. Therefore, this step was omitted.

The population selected for testing the survey instrument was the same as that used for testing the hypothesis.

FORMATTING AND DELIVERY

With respect to scaling of the quantitative/measurement instrument, both a 20-point scale and a 7-point Likert scale were tested. Callers were able to respond to the questions using either scale with similar ease and lack of confusion. However, the Ethics Committee strongly recommended that a 5-point Likert scale be adopted for ease of use over the telephone. The response options used were (1) strongly disagree, (2) disagree, (3) can't decide (no opinion), (4) agree, and (5) strongly agree. (Nelson, 1980) The questions were framed positively and balanced such that a selection of "5" was always an improvement in the score. Therefore, the maximum possible score for each domain were as follows: knowledge (20), perceived legitimacy (20) and sense of empowerment (15). The satisfaction survey, which was not part of the DTSM measurement instrument, also followed the same format. With five questions, the maximum possible score was 25.

The final measurement instrument and qualitative questions covering other aspects of DTSM behaviour questions were combined forming the Study Survey Instrument. The Study Survey Instrument was incorporated into a Data Collection Form (see Appendix 3) that was divided into two parts. The first part of the Data Collection Form included the text to be used to secure informed consent and a transcript for directing the investigator in completing the pre-counselling part of the Study Survey Instrument. The Ethics Committee requested that the informed consent not disclose too many details about the study because the information might bias the participant's response. The second part included a transcript for completing the longer post-counselling part of the Study Survey Instrument that included the satisfaction survey and open-ended questions about the counselling experience. A script was used to help ensure consistent delivery of the questions,
to minimize inter-counsellor differences and to reduce response bias. (Guyatt et al, 1989) The Motherisk advice given to callers was relatively consistent because it was based on the prepared Motherisk statements. See Appendix 5 for a sample of Motherisk statements.

Both Motherisk counsellors who were acting as investigators in the study had an opportunity to review and critique the final draft survey instrument including the script and the method of delivery and data collection, prior to study initiation. The counsellors selected for the study were trained to provide risk-counselling over the phone and had more than two years of experience.

The survey instrument was formatted for delivery over the telephone because it would have been too time-consuming and expensive to ask callers expecting information over the telephone to travel into the City of Toronto for a clinic visit just to complete a questionnaire.

FREQUENCY OF QUESTION ENDORSEMENT

The frequency of endorsement of each question choice was calculated by determining the proportion of callers choosing each of the response options; 1, 2, 3, 4 and 5. Normally, questions with endorsements between 0.2 and 0.8 are used.

SURVEY INSTRUMENT VALIDATION

Content (face, coverage and relevance) validity

The selection of domains was made based on literature concerning Drug Therapy Self Management. The background for the dimensions chosen has been reviewed in preceding section. The relevance, coverage, face, and content validity of the preliminary set of questions was reviewed and assessed in discussion with clinical or scientific experts. Criterion-related validity could not be established because there was no comparable scale for measuring DTSM in a teratogen-information centre.

The number and background of reviewers were:

- Motherisk staff (director, associate director, assistant director, two counsellors)
Scientific Review Committee represented by members of the Clinical Epidemiology Rounds group (presentation and discussion as part of the ethics review)

Social and Administrative Pharmacy Group

A pregnant woman

A graduate student in sociology

Ethics Committee (the committee and scientific liaison)

Not all reviewers were involved at each stage of development of the survey instrument.

Support for each chosen dimension is presented below.

The questions in the “Previous Advice” section were asked in order to obtain information on who might be providing competing information and were chosen empirically. According to De Geest et al (1994), vicarious experience (receiving advice) is a source of self-efficacy. Another possible source of information would be any previous experience a caller had had in calling Motherisk for information. This type of self-efficacy information is called a performance accomplishment.

Questions assessing knowledge were based in part on those found in a measurement instrument developed by Marshman (1997). The first question on chances of birth defects was taken from the questionnaire that was being used in the Motherisk clinic. The concept of partial information exists and is represented in the second question about having enough information. (Leclercq, 1995) According to Imanaka et al (1993), a patient’s satisfaction with information is directly affected by cognitive understanding; so a question on understanding the information was included. A question on the adequacy or reliability of the information was not included because callers would not likely have a basis for making that type of decision. Instead, a question on trusting the advice given was used.

In the domain of perceived legitimacy, the degree of satisfaction with the medication before pregnancy was important to assess because if the caller was unsatisfied before pregnancy it would be unlikely that she would be satisfied after becoming pregnant. Satisfaction with the medication
for the patient's medical condition was used as the surrogate for the patient's own risk/benefit analysis based on the assumption that if the perceived benefits outweighed the perceived risks the patient would be more likely to think that the medication was appropriate for her condition. (Imanaka et al, 1993; Redland et al, 1993) Because patients judge the effectiveness of therapy against achieving certain outcomes (Conrad, 1985), a question on using the drug to stay healthy was used. To pursue this avenue further, a question was added on keeping the baby healthy as a legitimate reason to take the drug.

Questions on empowerment were partially based on a measurement instrument by Marshman (1997). Questions on the "right to decide to take the medication" or "how much" were included to determine if callers felt empowered to make their own decisions. Because empowerment arises in part from the relationship with the provider (McCann et al, 1997), callers were asked whether they had a right to question their doctor about the safety of taking the medication in question during pregnancy.

Drug therapy self-efficacy though important was not included in the measurement instrument because of the difficulty in designing an appropriate series of questions that could be administered over the telephone.

The drug usage decision section encompassed both quantitative and qualitative aspects. Questions about drug usage before and during pregnancy were asked to identify patients that changed their drug usage. To assess whether they had made the decision independently, callers were also asked if anyone had recommended any drug usage changes. (Sackett et al, 1991) Callers were also asked whether the change in medication usage affected their health. In this way information was obtained on callers' physiological state as a source of self-efficacy, for comparison with medication usage. (De Geest et al, 1994)

According to the literature, aspects of a satisfaction survey should include whether the service is being delivered appropriately (e.g., amount of contact with counsellor, behaviour of counsellors), is equally accessible to all callers, or is following an acceptable process. (Barker et al, 1994) Imanaka et al (1993) published an instrument developed by Hall that had 12 questions and
an internal consistency reliability of 0.87. Five of these question-types were used for this study instead of 12 because the interaction with the counsellor is too brief to evaluate all aspects of satisfaction.

Appropriate delivery of service was surveyed by asking whether the counsellor had spent enough time in explanations and had a caring, respectful attitude. Accessibility of service was probed using a question about convenience of service. There was a final question specifically asking about overall satisfaction with the service received. Callers were then asked whether they had any comments about their experience with calling Motherisk just in case the questions were not sufficient.

At the end of the post-counselling interview, several callers were asked, "Has Motherisk counselling changed or influenced the way you feel about taking drugs during this pregnancy? Of what value was the service to you?" The responses and comments were documented and summarized.

In conclusion, given the requirement primarily for content validity, and the extensive review of the instrument by experts in the field, this instrument was considered to have adequate validity to proceed with the exploratory study.

Preliminary construct validity testing was performed as a way to explore the correlation between DTSM characteristics and to determine if accurate predictions could be made based on the model used.

Reliability Testing

To assess reliability one set of 5 patients answered the survey instrument before Motherisk counselling on two occasions, one to two weeks apart. The first and second set of scores for all patients were tested for association using the non-parametric Spearman rank correlation test. The conventional correlation coefficient (Pearson's product-moment correlation coefficient) was not used because the variables measured did not follow normal distributions. (Hassard, 1991) As an overall estimate of reliability, the coefficient of variation was calculated for each domain (pre-test,
post-test, change). For internal consistency, Cronbach's alpha was determined for each domain, both pre- and post-test, from aggregate scores of all participants.

Responsiveness and Reproducibility

Responsiveness and reproducibility were assessed as follows. Patients were divided into two groups, non-changers and changers. Non-changers were defined as participants who had the same intention to use their chronic medication, before and after Motherisk counselling. Changers were defined as participants who had a different intention to use their chronic medication, before and after Motherisk counselling. The data from non-changers (stable) were used to estimate reproducibility. The data from changers (unstable) were used to assess responsiveness.

Reproducibility of the measurement instrument was assessed by examining changes in the domain scores in non-changers as described above. For each of the three domains both the paired t-test and the Wilcoxon Signed Ranks Test were used to compare baseline to follow-up scores. A statistically significant result indicates that a change in score occurred that was unlikely to have occurred by chance alone, and suggests that scores for that domain of the instrument are not reproducible in the study population. Reproducibility was also assessed by calculating the within-person coefficient of variation defined as the standard deviation of stable subjects divided by the mean of the pre- and post-counselling scores.

Responsiveness was determined from unstable patients (changers) by examining the consistency of changes in each domain. (Guyatt et al, 1989) A probability value from a paired t-test and the Wilcoxon signed rank test was used to determine the probability that the difference occurred by chance. A statistically significant result means that the results did not occur by chance alone. Responsiveness was also assessed by calculating the ratio of the change occurring in changers (unstable patients) to the standard deviation of changes in non-changers (stable patients). The larger the ratio, the smaller the sample size needed to show the change. (Guyatt et al, 1989, pg 807) If the ratio is greater than one then the number of subjects per group required to detect a change, is less than 20. (Guyatt et al, 1989)
Effect size, defined as the mean change in the score divided by the standard deviation of the measure, was the final measure of responsiveness used. A score of 0.8 was considered a large effect size. (Cohen, 1977)

EXPLORATORY STUDY

This study was exploratory in that the characteristics of subgroups as well as the potential relationships between the variables of knowledge, legitimacy, empowerment and DTSM were being investigated. The measurement part of the survey instrument was analyzed as an ordinal scale requiring non-parametric (distribution-free) methods of analysis and as an interval scale requiring parametric analysis. Because this was a correlational study, simple statistical measures of association (e.g. chi-square and correlation coefficients) were used.

The goal of the study was to enroll at least 25 patients to test the survey instrument and to obtain preliminary information on the effects of Motherisk counselling on attitudes towards DTSM. The study was approved by the Hospital for Sick Children(Toronto) Research Ethics Committee on August 28, 1998. A modification was approved on October 30, 1998.

To determine the number of patients who would meet the inclusion criterion of taking a chronic medication during the first trimester, all questions were reviewed over a one-week period. Over five days, approximately 550 patients contacted Motherisk; 62 patients met the inclusion criteria. Based on the premise that 5 counsellors respond to calls for 4 out of 5 days each week, that each counsellor answers an average of 110 calls per week, and that callers could not be screened during busy times, it was anticipated that each counsellor/investigator would be able to screen about 4 calls each week. Based on this information, the study was expected to take at least two months.

SELECTION OF SUBJECTS

The population of interest was pregnant women who contacted the Motherisk service in Toronto. Motherisk callers constitute a relatively healthy, well-educated population who follow good health practices and are relatively experienced in dealing with the health care system. (Redland et
However, to limit the context further for making a medication usage decision and assessing DTSM in pregnancy, the study population was more narrowly defined to include only those with a chronic medical condition needing chronic treatment. Long-term medication-usage decisions most likely differ from short-term use decisions for an acute condition. For acute conditions, callers would already have received some treatment and would be more concerned about the effects of past exposure; the consequences of stopping treatment would not be as great as it would be in a chronic condition. For chronic conditions, callers must deal with the effects of past exposure and future exposure; the potential effect on their future health is greater and likely involves more aspects of DTSM.

Patients taking a teratogenic drug were excluded from the study. They have different kinds of decisions to make (e.g. termination of the pregnancy, stopping the drug etc.) and are handled differently at Motherisk.

The timing of medication was restricted to the first and second trimester because some drugs that are acceptable for chronic use in the first two trimesters of the pregnancy are not acceptable in the last stages of pregnancy. Mixing participants from all stages would have resulted in a more heterogeneous population and results that would have been more difficult to interpret.

Motherisk accepts calls every weekday between 9am and 5pm. Callers to the centre are put on hold until a counsellor is available. Calls are answered consecutively. The counsellor does not have an ability to select calls but receives them randomly according to his/her workload and availability. Participants were admitted into the study in the order in which they called Motherisk. Because the number of callers expected to meet inclusion/exclusion criteria was low, every caller received by the study investigators who met the criteria was asked to participate in the study. This type of sampling usually has the unbiased characteristics of a random sample. (Hassard, 1991)

**Inclusion Criteria**

The inclusion criteria, for the study for the Study Subgroup CMU-BR (see Figure 2 – Box 2f), were the following:
1. Women who call Motherisk seeking information on the risk to their fetus of exposure to their prescription medication.

2. Women taking a drug believed not to increase the risk of fetal malformations above the baseline risk of 1-3% according to the Motherisk statements.

3. Women bearing a fetus between 2 weeks and 14 weeks of gestation. [Amended later to include fetuses between 2 weeks and 28 weeks of gestation.]

4. Women able and willing to provide verbal informed consent to participate in the study.

5. Women who report having a concurrent medical condition for which medication has been prescribed and which is expected to be required for the remainder of the first trimester or for at least two weeks more, whichever is greater.

6. Able to communicate in English.

Exclusion Criteria

The exclusion criteria, for the study for the Study Subgroup CMU-BR (see Figure 2 – Box 2f), were the following:

1. Women who seek information about the risk presented by an illicit drug in addition to the prescription medication described above.

2. Women who would be unavailable for follow-up by telephone.

PROCEDURES

Subject Interview

Two Motherisk counsellors were enlisted to identify potential participants following completion of the Motherisk intake form, to obtain informed consent, to enroll patients into the study, and to administer the pre-counselling part of the Study Survey Instrument to participants as outlined and scripted on the Data Collection Form. (See Appendix 3) Following the study procedures all participants received routine risk-counselling according to the standardized
Motherisk statements prepared by Motherisk staff. (See Appendix 5) To avoid bias, a third counsellor/investigator administered the post-counselling part of the Study Survey Instrument. Verbal informed consent to participate in this post-counselling portion of the study, answers to survey instrument questions, and any additional comments from participants were also documented on the Data Collection Form. Subjects were contacted for the post-counselling session at least seven days after the pre-counselling session to reduce the chance that they would remember their first set of responses. A maximum time limit between calls was not established but it was understood that reliability would decrease over time.

The total time required for participation in the study from each participant enrolled was about 10 minutes for the pre-counselling session and about 10 minutes for the post-counselling session according to measurements made of elapsed time.

The counsellors followed the procedure below: (all Boxes refer to Figure 2)

1. Completed the regular Motherisk intake form but gave no Motherisk advice. (Box 2b)

2. Assessed the caller for inclusion/exclusion criteria. (Box 2g)

3. If the patient met the criteria, asked the caller if she was interested in hearing about a study for possible participation. (Box 2g)

4. Explained the study and then if the caller agreed obtained informed consent. (Box 2g)

5. If informed consent was not given (Box 2h), the caller received routine Motherisk information and counselling. (Box 3c)

6. If informed consent was given by the caller, the Study Survey Instrument was administered as per the Data Collection Form. (Box 2i)

7. All participants were asked to give a phone number at which they would be available for a follow-up telephone call after counselling or a clinic visit.

8. After the study interview, study participants were give the routine Motherisk information and counselling. (Box 2i)
9. All participants were given the opportunity to attend clinic. (Box 2i)

10. If phone counselling was given and a clinic visit was not accepted (Box 2i), the participant was called again in 5-7 days by the third counsellor and the second part of the Study Survey Instrument was administered. (Box 2m)

11. If a clinic visit was accepted, the visit was scheduled. (Box 2k)

12. All participants attending clinic (Box 2o) were called 5-7 days after the clinic visit by the third counsellor and administered the second part of the Study Survey Instrument. (Box 2m)

13. All participants failing to attend clinic (Box 2l) were called 5-7 days after the clinic visit and the post-study portion was repeated. (Box 2k)

Withdrawal of Patients from the Study

Participants were withdrawn or removed from the study for any of the reasons stated below.

1. Participant requested withdrawal for any reason.

2. Participant chose not to answer the questions.

3. Development of any conditions identified in the exclusion criteria.

DATA COLLECTION

Extraction of data from documentary Motherisk records

Callers' basic demographic information and personal history were collected in an effort to better understand the decision context. Environmental factors and personal attributes appeared to be more difficult to study over the telephone so this data was not collected. Personal values such as those concerning birth defects and pregnancy termination were deemed too sensitive to discuss during a quick telephone interview; worse, callers might have felt that their personal values were being questioned. Therefore, this information was not collected either.
For all subjects entered into the study, the Motherisk Telephone Intake Forms were collected and the information contained therein, entered into a database. The following information was extracted from the Motherisk Telephone Intake Form:

- caller's name and telephone number
- age
- the person who referred her to the service
- gestational history
- duration of pregnancy, date of last menstrual period
- recreational drug use (cigarettes, alcohol, illicit drugs)
- targeted concomitant diseases
- concomitant drug use (exposure details)
- drug/exposure of concern
- advice given to patient
- date of clinic appointment or referral

The following additional information was extracted from the Motherisk Clinic Record and Interview Form for those participants attending the Motherisk clinic (See Figure 2 - Box 20):

- obstetrical history
- visual analog scale before and after clinic visit for 1) tendency to continue or terminate pregnancy 2) patient's perception of risk of major birth defects in the fetus 3) patient's perception of baseline risk for birth defects in general population

Collection of data from the survey instrument

All responses to the Study Survey Instrument were documented on the Data Collection Form (see Appendix 3) which was not made available in any form to a third party. All participants'
data were entered into a spreadsheet along with data from the Motherisk intake form. Patients were identified by initials, birth date and subject number only.

DATA ANALYSIS

Outcome variables

The medication usage intent (dose level maintained, decreased or increased) was the primary outcome variable. The effect of Motherisk counselling on DTSM attitudes (measurement instrument) was the secondary outcome variable.

Criteria for effectiveness of Motherisk

The minimally important difference or even the expected difference between pre-counselling study survey instrument results and post-counselling results was unknown prior to study start. However, pre-study it was hypothesized that Motherisk counselling would be effective if participants continued to take their chronic medication as they had prior to becoming pregnant.

Data sets analyzed

Data from all patients who completed the Study Survey Instrument over the phone before and after counselling were included in the analysis.

Statistical analysis

All tests were considered significant at a p level of < 0.05.

Patient demographics & characteristics

Demographic and baseline characteristics were examined using descriptive statistics based on age, the person who referred the patient to Motherisk, number of previous pregnancies, date of the last menstrual period, and a limited medical history (administered using a short yes/no checklist). The information on drug use included the drug name, date started, date stopped, dose, route and indication.
Interval or ratio variables were summarized according to their mean, median and range.

A post-hoc analysis of preexisting patient characteristics was planned to provide an explanation for variations in outcomes, within and between patient groups.

The proportions of callers in each subgroup were compared using Chi squared tests.

**Chronic Medication Dosing**

Medication dosing data was ordinal in nature. Results for chronic medication dosing were categorized as taking the same amount, less or more of the prescribed medication. Dosage changes were then further broken down into patients acting on their own or patients acting on the advice of a health care professional. Therefore, McNemar's test, which is appropriate for comparisons between 2 dependent groups, was used.

**Satisfaction Survey**

Each of the five questions in the satisfaction survey had a possible score of between one to five. The total score was calculated as the sum of all five questions for a maximum possible score of 25. All participants were asked an open question, “Do you have any comments about the Motherisk service?”. The qualitative responses were recorded and summarized.

**Measurement Instrument analysis**

Each item in each domain was weighted equally and summed to form a domain score. When more than one answer was permissible (as for the fourth question under the Knowledge domain) (see Appendix 2 – Data Collection Form page 2, knowledge, question (d)), the response was calculated as an average of the score for all responses. All items were scored on a scale from one to five with a higher score indicating a better outcome according to the hypothetical model of the factors involved in DTSM. Missing values were estimated by substituting the mean from a scale's non-missing items calculated on an individual basis.

The measurement scale used numbers that were not categorical and were more than just a set of ranks even though the exact distance from one point to another was not known. Under these
conditions, psychological scales can be treated as interval scales. (Nunnally, 1978) It was unclear before study start whether the assumptions of parametric testing would be met. Therefore, both non-parametric and parametric testing were planned. For parametric testing, the t-test for dependent samples design was to be applied (May et al, 1990) This is a repeated measures design in which a single subject contributes two scores. It tests the difference between paired scores. For non-parametric testing, the Wilcoxon Matched Pairs Signed Rank Test was to be applied. A rank less than or equal to the tabulated critical value indicates that the null hypothesis should be rejected at the corresponding level of significance. (Hassard, 1991) The two-sided test was used because the score could have gotten better or worse following Motherisk counselling.

The difference in scores for each domain, from baseline to post-counselling, was calculated for each of the following groups:

- those receiving telephone counselling alone
- those receiving telephone counselling and attending a clinic visit

Within each group, the observations were dependent; therefore, a t-test for paired samples (matched pair t-test) was used for parametric testing and the Wilcoxon signed ranks test for non-parametric testing.

**Sample size determination**

There was one dependent group for the primary effectiveness variable tested. Given that this was an exploratory study in an unstudied patient population it was not possible to predict the relative intervention effect or variability as needed to estimate the required sample size. Therefore, a sample size of 25 was selected as the minimum acceptable number considered adequate to detect a large effect size according to the method of Cohen. (Cohen, 1977) In this method, a large treatment effect is arbitrarily defined as one in which the treatment difference equals or exceeds three-quarters of the standard deviation of the measurement involved. (Hassard, 1991, pg 171) More precise estimates of the magnitude of variation involved, and the sample size required, are possible once results from the measurement instrument are obtained. However, because the effect
size was unknown at the commencement of the study, as many participants as possible over a 2-month period were surveyed to achieve a minimum of 25 participants and a maximum of 100 participants (for reasons of time/resource constraints).

**Subgroup analysis**

Patients’ attitudes depend on the purpose for their call to Motherisk. The following subgroups were identified at study start.

- those calling for information on their own
- those directed to Motherisk by a physician

**Assumptions**

Because no attempt was made to verify the background information provided by callers, the following assumptions were made.

- callers were giving accurate information concerning their diagnosis and prescribed drug use
- the disease diagnosis was correct and nontrivial
- therapy was effective
- the caller was informed and willing. (Sackett et al, 1991)

**ETHICS BOARD APPROVAL**

Approval for the proposed exploratory study was granted by the Research Ethics Board of the Hospital for Sick Children. (see Appendix 4)
SECTION 3 RESULTS

PARTICIPATION RATE

Figure 4 below describes study subjects as a proportion of the total number of callers (estimated) to Motherisk over the study period of 105 days.

![Diagram of study population sampling](image)

<table>
<thead>
<tr>
<th>Total Number of Callers*</th>
<th>Chronic Medication Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,420</td>
<td>8503 (81.6%)</td>
</tr>
</tbody>
</table>

- **Baseline Risk**: 1771 (92.3%)
- **Increased risk**: 146 (7.6%)

Of the callers approached, the participation rate was almost 100%. Although the exact number of callers refusing to participate was not recorded, the counsellors estimated that there were two. In addition, there were three other callers who gave their consent to participate but who were then excluded from completing the first study survey. (See Figure 5) The most common reasons for excluding callers from study participation was the inability of callers to understand English sufficiently and lack of co-operation in answering the questions.
Of the 49 Motherisk callers who completed the post-counselling survey, only one caller\(^1\) returned for a clinic visit making any statistical analysis or comparison of her outcomes with the rest of the callers meaningless.

Seven participants (12.5\%) who answered the pretest failed to answer the posttest for the following reasons:

1. One caller agreed to the study but was hesitant when completing the pretest interview. She lived in a group home. When attempts were made to call her for the post-test, the telephone was seldom answered and she never returned messages.

2. After completing part of the pretest survey instrument one caller became angry. She thought the questions were silly and redundant but chose to continue. When the post-test counsellor encountered the same problems the caller was advised that her participation was being discontinued and that her data collected to date would be destroyed.

\(^1\) She had been diagnosed with rheumatoid arthritis for which she had been taking prescribed medication for eight months. Upon finding out she was pregnant she stopped all her medication. Prior to Motherisk counselling her scores were: Knowledge 15, Perceived Legitimacy 7 and Empowerment 10. Following Motherisk counselling her scores were 25, 10 and 11, respectively. Both her rheumatologist and doctor said that it would not be safe to take her arthritis medication during pregnancy.
3. The telephone number for one participant was incorrect and she could not be contacted for the post-test.

4. One caller had a spontaneous abortion shortly after the first interview and declined to continue with the post-test.

5. One caller withdrew consent without giving a reason.

6. One caller had a spontaneous abortion shortly after the first interview and declined to continue.

7. One caller went on sick leave shortly after the first interview and only left her office phone number with the Motherisk counsellors. Although her work advised the interviewer that she was on leave they would not give out her home phone number. Therefore, she was lost to follow-up.

PARTICIPANT CHARACTERISTICS AT BASELINE

A total of 49 subjects participated in this research. Their baseline characteristics are presented in Tables 2 and 3 below. Included, is a comparison of selected characteristics to a sample (5 days) of the Motherisk population over the same time period as well as a sample of non-pregnant callers (5 days) requesting information on drugs for planning purposes.

Table 2: Characteristics of the study group, a sample of the overall population of Motherisk callers and a subgroup of callers planning a pregnancy.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>&lt;20</th>
<th>0 (0%)</th>
<th>4 (0.8%) (NSS)*</th>
<th>0 (0%) (NSS)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25</td>
<td>7 (14.6%)</td>
<td>40 (8.0%) NSS*</td>
<td>1 (2.5%) NSS*</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>15 (31.3%)</td>
<td>114 (22.8%) NSS*</td>
<td>8 (20%) NSS*</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>20 (41.7%)</td>
<td>215 (43.1%) NSS*</td>
<td>16 (40%) NSS*</td>
<td></td>
</tr>
<tr>
<td>36-40</td>
<td>5 (10.4%)</td>
<td>105 (21.0%) NSS*</td>
<td>10 (25%), p&lt;0.01*</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>1 (2.1%)</td>
<td>25 (5.0%) NSS*</td>
<td>5 (12.5%) NSS*</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean age (yrs)</td>
<td>Median age (yrs)</td>
<td>Median gestational age (weeks)</td>
<td>Referred by:</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>30.5 (range 20-43)</td>
<td>32.5 (range 15-51)</td>
<td>33.9 (range 23-48)</td>
<td></td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Identity of Caller</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>49</td>
<td>496</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Friend/Family</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Health professional</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gestation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>44 (92.6%)</td>
<td>239 (48.6%), p&lt;0.01%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second &amp; Third Trimester</td>
<td>4 (8.2%)</td>
<td>252 (51.4%), p&lt;0.01%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>10</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Mean gestational age (weeks):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>self/called before</td>
<td>12 (24.4%)</td>
<td>204 (45.3%), p&lt;0.05*</td>
<td>15 (40.5%)</td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>30 (61.2%)</td>
<td>152 (33.8%), p&lt;0.01%*</td>
<td>17 (45.9%)</td>
<td></td>
</tr>
<tr>
<td>family/friend</td>
<td>3 (6.1%)</td>
<td>31 (6.9%) NS*</td>
<td>2 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>other health professional</td>
<td>4 (8.2%)</td>
<td>51 (11.3%) NS*</td>
<td>2 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>magazine, pamphlet, book, newspapers</td>
<td>0</td>
<td>12 (2.7%) NS*</td>
<td>1 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>51</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td>22 (45.8%)</td>
<td>239 (48.2%) NS*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First pregnancy</td>
<td>26 (54.2%)</td>
<td>257 (51.8%) NS*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>5</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Previous SA</td>
<td>7 (14.6%)</td>
<td>34 (6.9%) (1-7) NSS*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Medical Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Callers with a medical condition</td>
<td>49 (100%)</td>
<td>501 (100%)</td>
<td>40 (100%)</td>
<td></td>
</tr>
<tr>
<td># Callers with a chronic medical condition</td>
<td>49 (100%)</td>
<td>146 (29.1%), p&lt;0.01*</td>
<td>22 (55%)</td>
<td></td>
</tr>
<tr>
<td># Callers with &gt;1 chronic medical condition</td>
<td>14 (28.6%)</td>
<td>19 (3.8%), p&lt;0.01*</td>
<td>8 (20%)</td>
<td></td>
</tr>
<tr>
<td># chronic Medical conditions (total)</td>
<td>67</td>
<td>168, p&lt;0.01*</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td># of chronic Medical Conditions per caller</td>
<td>1.4</td>
<td>0.3</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Type of question</td>
<td>Herbal</td>
<td>8 (2%) NSS*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>-------------</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>1 (1.8%)</td>
<td>41 (7.8%) NSS*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td>3 (5.4%)</td>
<td>59 (11.3%) NSS*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>49 (87.5%)</td>
<td>382 (73%), p&lt;0.01*</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (5.4%)</td>
<td>34 (6.5%) NSS*</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numbers of questions</th>
<th>Total # of questions for all callers</th>
<th>92</th>
<th>718</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average # questions per caller</td>
<td>1.9</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Drug Questions</td>
<td>Number of calls - single drug</td>
<td>30 (61.2%)</td>
<td>244 (48.7%)</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td></td>
<td>Number of calls - multiple drugs</td>
<td>19 (38.8%)</td>
<td>138 (27.5%)</td>
<td>14 (35%)</td>
</tr>
<tr>
<td></td>
<td>Total number questions about drugs</td>
<td>84</td>
<td>576</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Average # drugs/drug caller</td>
<td>1.7 (1-8)</td>
<td>1.5 (1-7)</td>
<td>1.8 (1-6)</td>
</tr>
<tr>
<td>Chronic Drugs</td>
<td># Women on Chronic Drugs</td>
<td>49 (100%)</td>
<td>92 (18.4%), p&lt;0.01*</td>
<td>21 (52.5%)</td>
</tr>
<tr>
<td></td>
<td>Total # chronic drugs taken by all women</td>
<td>74</td>
<td>135</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Average # chronic drugs per woman</td>
<td>1.5</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td># women taking a psychotropic</td>
<td>32 (65.3%)</td>
<td>18 (19.6%) p&lt; 0.01*</td>
<td></td>
</tr>
<tr>
<td></td>
<td># chronic drugs taken without increase risk</td>
<td>70</td>
<td>126</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td># chronic drugs without risk as % of total # chronic drugs</td>
<td>94.6%</td>
<td>93.3%</td>
<td>81.6%</td>
</tr>
<tr>
<td></td>
<td># patient on drugs without increased risk</td>
<td>45 (91.8%)</td>
<td>85 (17%), p&lt; 0.01*</td>
<td></td>
</tr>
</tbody>
</table>

| Duration of Drug Use | Duration of Use of Drug Identified for This Study (N=49) | 1 week to 12 years | n/a | n/a |

*Chi-squared test for association selected sample of pregnant callers, the selected sample of planning women, and the study sample
NSS – Not statistically significant n/a – Not applicable # - Number

Of the 204 callers from the sample population who were not referred by someone, 189 had actually called before. Additionally, of the 382 callers asking a drug risk question, 190 (49.7%) had not yet taken the drug but had called for planning purposes.
Table 3: Study medications and medical conditions of study participants.

<table>
<thead>
<tr>
<th>Study Medical Condition</th>
<th>Gastrointestinal</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunologic/allergic</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Neurologic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Psychiatric</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unspecified Skin Condition</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sleep Disorder</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Drug - Classification</th>
<th>Antidepressant</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antidiarrheal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Antihistamine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Antimalarial</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Antimigraine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Antiviral</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>B-agonist</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>B-blocker</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>GI motility</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>H2 blocker</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Muscle relaxant</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sedative/hypnotic</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Thyroid replacement</td>
<td>1</td>
</tr>
</tbody>
</table>

SURVEY INSTRUMENT VALIDATION

FREQUENCY OF ENDORSEMENT

Study participants endorsed each scale selection at least once at the 20%-80% rate in every domain either pre-counselling or post-counselling. (See Table 4) This evidence supports the use of a 5-point scale.
Table 4: Frequency (percentage) of endorsement of each question in the study measurement instrument.

<table>
<thead>
<tr>
<th>Question Number</th>
<th>Knowledge Domain (number of times endorsed (%))</th>
<th>Perceived Legitimacy Domain (number of times endorsed (%))</th>
<th>Empowerment Domain (number of times endorsed (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;2</td>
<td>5 (10.2)</td>
<td>1 (2.1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>6 (12.2)</td>
<td>2 (4.2)</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>33 (67.3)</td>
<td>3 (6.1)</td>
<td>24 (49)</td>
</tr>
<tr>
<td>4</td>
<td>4 (8.2)</td>
<td>16 (32.7)</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>5</td>
<td>1 (2)</td>
<td>26 (53.1)</td>
<td>7 (14.2)</td>
</tr>
</tbody>
</table>

1 Scale selection: 1 (strongly disagree), 2 (disagree), 3 (unsure), 4 (agree), 5 (strongly agree)

RELIABILITY TESTING

The test-retest correlations for each domain were as follows: knowledge ($r_s = 0.70$), perceived legitimacy ($r_s = 0.70$) and sense of empowerment ($r_s = 0.95$). The correlation coefficients for the knowledge and perceived legitimacy domain were within the acceptable range of 0.7 to 0.9. The correlation for empowerment was higher than expected.

The coefficients of variation for each domain (pre-test, post-test, change), an index of the relative dispersion of the data set, are summarized in Table 5. A coefficient of variation less than 1.0, as occurred for the pre-test and post-test scores, indicates compact data.
Table 5: Calculation of the coefficient of variation for each domain as an estimate of reliability (N=49).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pretest</th>
<th>Posttest</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge (range of 0-20)</td>
<td>4 - 16</td>
<td>9.8</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>8 - 20</td>
<td>14.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>-4 - 14</td>
<td>5.1</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Perceived legitimacy (range of 0-20)</td>
<td>4 - 20</td>
<td>13.3</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>7 - 20</td>
<td>13.4</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>-9 - 7</td>
<td>0.16</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Empowerment (range of 0-15)</td>
<td>5 - 15</td>
<td>11.5</td>
<td>2.76</td>
</tr>
<tr>
<td></td>
<td>7 - 15</td>
<td>11.5</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>-5 - 5</td>
<td>0</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1</td>
<td></td>
</tr>
</tbody>
</table>

According to the internal consistency coefficients (Cronbach's alpha) for each domain, both pre-test and post-test, (see Table 6) the homogeneity of items post-counselling was within an acceptable range for the domains of knowledge and perceived legitimacy post-test but was outside the established limits of 0.7 to 0.9 for the sense of empowerment domain.

Table 6: Values of Cronbach's alpha for each domain of the study measurement instrument, pre-counselling and post-counselling.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-test</td>
<td>0.50</td>
</tr>
<tr>
<td>Post-test</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>0.74</td>
</tr>
</tbody>
</table>

From the 49 participants, 32 patients were classified as non-changers (stable subjects who did not change the way they were taking their chronic medication following Motherisk counselling) and 17 were classified as changers. Reproducibility testing in non-changers showed that all domains changed between the pre-test and post-test, and these changes were unlikely to have occurred by chance alone. (See Table 7) This indicates a lack of reproducibility for the knowledge and perceived legitimacy domains, according to non-parametric testing, when using the criterion of drug usage intention to define a non-changer.
Table 7: Reproducibility assessment by examining changes in the domain scores of the measurement instrument in participants with medication usage intentions remaining the same pre- and post-counselling (non-changers) (N=32).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Score</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>9.9</td>
<td>14.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>13.1</td>
<td>13.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Empowerment</td>
<td>12.2</td>
<td>11.1</td>
<td>-1.1</td>
</tr>
</tbody>
</table>

Another component of reproducibility is the variability in scores in stable subjects over time. By comparing the standard deviation of changes in response to each question in all stable subjects, to the mean score of the pre- and post-test, a within-person coefficient of variation was calculated. (Guyatt et al, 1989) See Table 8. The within-patient coefficient of variation ranged between 0.22 and 0.32. The smaller the value, the more reproducible the results from that particular domain of the measurement instrument.

Table 8: Reproducibility assessment by calculating the within-person coefficient of variation in stable participants (non-changers) (N=32).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>±3.9</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>±2.8</td>
</tr>
<tr>
<td>Empowerment</td>
<td>±2.5</td>
</tr>
</tbody>
</table>

The measure of responsiveness that relates the magnitude of the difference in subjects who are clinically changed to the standard deviation of changes in stable subjects (Guyatt et al, 1989, pg 807) is shown in Table 9. The greater the ratio, the smaller the sample size needed to show change. The results indicate that, for the knowledge domain, a sample size of less than 20 would be needed to detect a change.
Table 9: Responsiveness assessment by calculating the ratio of the difference in subjects who were unstable (changing) to the standard deviation of changes in stable (unchanging) subjects.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>±3.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>±2.8</td>
<td>-0.1</td>
</tr>
<tr>
<td>Empowerment</td>
<td>±2.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Results of testing responsiveness by examining the consistency of changes in each domain from unstable patients (changers) showed that the measurement instrument was sufficiently sensitive in identifying changes in the knowledge and empowerment domains in participants who changed their intention to take their medication pre-counselling versus post-counselling. See Table 10.

Table 10: Responsiveness assessment by examining changes in domain scores in participants with unstable responses (changers). (N=17)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pre-test</th>
<th>Post-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>9.55</td>
<td>15.06</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>13.53</td>
<td>13.24</td>
<td>NS</td>
</tr>
<tr>
<td>Empowerment</td>
<td>10.29</td>
<td>11.71</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

*Repeated administration of the DTSM instrument in 17 subjects who did change from pre-test to post-test.

Responsiveness was also measured by effect size. See Table 11. Results show a moderate to large effect size for the knowledge domain.

Table 11: Effect size for each domain and total score of the DTSM instrument as an estimate of responsiveness. (N=49)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>5.13/3.8= 1.35</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>0.16/3.35= 0.05</td>
</tr>
<tr>
<td>Empowerment</td>
<td>0.02/2.18= 0.01</td>
</tr>
</tbody>
</table>
CONSTRUCT VALIDITY

The following ex ante predictions concerning responses to the DTSM instrument, the corresponding correlation coefficient and the corresponding results are presented below.

1. Patients who call Motherisk on their own initiative rather than being referred should have a higher score in the empowerment domain, pre-counselling, than patients referred by someone else (extreme groups validity testing). Research shows that people will approach, explore and try to deal with situations within their self-perceived capabilities, and will avoid transactions with stressful aspects of their environment they perceive as exceeding their ability. (Rosenstock, 1985) Women who are able to speak with their doctor about their concerns should be more empowered. Therefore there should be a positive correlation between the empowerment score and self-referral. The predicted correlation was $0.3 \leq r < 0.4$. However, the actual correlation coefficient for the above was 0.09 (NSS) ($n=49$).

2. Patients who attend clinic visits rather than receiving only information over the phone should have a higher score in Knowledge domain. Patients who attend clinic visits should have a higher score in the knowledge-d questions (trust the advice I have received) (see Appendix 3) because they receive the information both over the phone from a counsellor and also in person from a physician in a hospital clinic. The personal reinforcement of the risk message might be expected to generate more trust on the part of the patient. The predicted correlation coefficients for both were $0.3 \leq r < 0.4$. However, only one patient attended clinic, so these predictions could not be tested.

3. In patients with a low rating (arbitrarily chosen as a mean score of 3 or less in each of the four dimensions for a total score of $\leq 12$ out of a maximum possible score of 20) in the total score for perceived legitimacy and a high rating in the total score for sense of empowerment ($\geq 12$ out of a maximum possible score of 15) pre-counselling, the correlation coefficient with not taking the drug as prescribed, was predicted to be moderate with $0.4 \leq r < 0.5$. One might expect that patients not convinced of a
medication's benefit and empowered to make decisions for themselves would choose not to take the medication.

There was a low correlation of 0.34 (p<0.05, N=49).

4. In patients with a high score in the total knowledge domain (arbitrarily chosen as a mean score of 4 or 5 in each of the four dimensions for a total score of ≥16 out of a maximum possible score of 20) post-counselling, the correlation coefficient with those taking at least some medication post-counselling was predicted to be high (r ≥ 0.5). If physicians believe that explaining the risks and complications of medication-taking and educating patients are the top two therapeutic measures that will improve compliance (Sackett et al, 1991), the score in the knowledge domain should correlate highly with those continuing to take their medication provided they believe the medication is worthwhile.

There was a high correlation of 1 (p<0.001, N=10) between patients scoring high in the knowledge domain (≥16) and taking at least some medication post-counselling.

5. A low correlation (0.3 ≤ r < 0.4) was predicted between the total empowerment scores (post-counselling) and the taking of at least some drug post-counselling in patients scoring high in the total empowerment domain (arbitrarily chosen as a mean score of 4 or 5 in each of the three dimensions for a total score of ≥12 out of a maximum possible score of 15). Participants that are empowered to make personal drug usage decisions should be in a better position to act on the risk information they receive to take a needed medication in pregnancy.

There was a low correlation of 0.30 (NS, N=22) between the total score in the empowerment domain and the intention to take at least some medication post-counselling.

6. Post-counselling, a moderate correlation of 0.4 ≤ r < 0.5 was predicted between patients with a high perceived legitimacy total score (arbitrarily chosen as a mean score
of 4 or 5 in each of the four dimensions for a total score of ≥16) and those taking their medication. The calculated value of the correlation coefficient was 0.45 (NSS, N=16).

7. Post-counselling, a high correlation of ≥ 0.5 was predicted for patients with a high perceived legitimacy score (arbitrarily chosen as a mean score of 4 or 5 in each of the four dimensions for a total score of ≥16 out of a maximum possible score of 20) and taking the study drug as prescribed before pregnancy. The calculated value of the correlation coefficient was 0.48 (NSS, N=16).

8. A moderate correlation (0.4 ≤ r < 0.5) was predicted between empowerment question number two (right to decide how much medication to take in pregnancy) post-counselling and changing medication use without a doctor’s advice post-counselling. The calculated value of the correlation coefficient was <0.1 (NSS, N=7).

9. A moderate correlation (0.4 ≤ r < 0.5) was predicted between patients with a DTSM total score ≥44 (arbitrarily chosen as a mean score of 4 or 5 in each of the eleven dimensions for a total score of ≥ 44) and taking drug post-counselling as before pregnancy.

The correlation was 0.49 (NSS, N=14).

10. Post-counselling, a moderate correlation (0.4 ≤ r < 0.5) was predicted between the total score in perceived legitimacy total and taking the drug as prescribed. The calculated correlation coefficient was 0.42 (p<0.005, N=49).

EFFECT OF MOTHERISK COUNSELLING ON DTSM ATTITUDES

The score for each of the three domains of the measurement instrument was calculated separately as was the total score. Every missing score was replaced by the average of the available scores for that domain. If 0 had been substituted for missing scores, the change scores would have been artificially increased. For the Knowledge domain, when there were two or more scores given for question #4, they were averaged to obtain a single score.
The time between the pre-test and post-test was a mean of 16.1 days (range 3-105). The median was 11.5. Although the plan was to phone callers back within 7 to 14 days, in practice callers were extremely difficult to contact even at the time and phone number specified. Reasons for delayed contact included sickness, unexpected absence from work (when a work number was given), incorrect phone numbers, holidays, busy schedules, hospitalisation, miscarriage, avoidance behaviour and care of other children requiring the investigator to call back.

Graphs of results before and after Motherisk counselling are presented in Figures 6 –8.

Figure 6: Total knowledge score (4 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).

Figure 7: Perceived Legitimacy Total (N=49).
Figure 7: Total perceived legitimacy score (4 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).

Figure 8: Total sense of empowerment score (3 dimensions) before (pretest) and after (posttest) Motherisk counselling (N=49).

See Appendix 6 for all before/after scores for each question in each domain.

The degree of correlation between the pre-counselling total score for each domain and the change in the total score post-counselling, was determined. Results (see Table 12) showed that there was a negative linear relationship between these two variables that was moderately large for the knowledge and empowerment domains; this result suggests that the higher the pre-counselling score the less the change in score post-counselling.

Table 12: Correlation between the pre-counselling total score for each domain and the change in total score post-counselling.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Correlation Coefficient</th>
<th>Before Post</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>0.45</td>
<td>-0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>0.16</td>
<td>-0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Empowerment</td>
<td>0.37</td>
<td>-0.60</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* proportion of variation common to or shared by both variables

The first part of the fourth objective was to determine the nature and extent of the effect, if any, of the MR service on factors influencing DTSM in the study population. The null hypothesis was that for each domain, the mean measurement instrument score pre-counselling would not differ from the mean measurement instrument score post-counselling.
The measurement instrument scores for all domains, separately and combined, from the quantitative part of the instrument are presented in Table 13. Results show that only for the Knowledge domain can the null hypothesis be rejected with the conclusion that there was a significant change in the score following Motherisk counselling.

Table 13: Changes in domain scores, separately and combined, pre- and post-counselling.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pretest</th>
<th>Posttest</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge (max score 20)</td>
<td>9.8</td>
<td>14.9</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>15</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>4 - 16</td>
<td>8 - 20</td>
<td>-4 - 14</td>
</tr>
<tr>
<td></td>
<td>±2.6</td>
<td>±2.9</td>
<td>±3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>13.3</td>
<td>13.4</td>
<td>0.2</td>
</tr>
<tr>
<td>(max score 20)</td>
<td>14</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4 - 20</td>
<td>7 - 20</td>
<td>-9 - 7</td>
</tr>
<tr>
<td></td>
<td>±3.4</td>
<td>±3.8</td>
<td>±3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Empowerment (max score 15)</td>
<td>11.5</td>
<td>11.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 - 15</td>
<td>7 - 15</td>
<td>-5 - 5</td>
</tr>
<tr>
<td></td>
<td>±2.8</td>
<td>±2.3</td>
<td>±2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Total Score (max score 60)</td>
<td>34.5</td>
<td>39.8</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>35.5</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>20-45</td>
<td>27-54</td>
<td>-11-20</td>
</tr>
<tr>
<td></td>
<td>±5.3</td>
<td>±6.2</td>
<td>±6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

When preliminary examination of the data indicated that the data were not normally distributed (see Figures 6-8), the decision was made to use non-parametric tests. Therefore, the data were analysed as paired data using the Wilcoxon Matched Pairs Signed Rank Test. (Hassard, 1991) (See Table 14)

Table 14: The Wilcoxon matched pairs signed rank test of scores for each domain and for the total score (N=49)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>1193.5</td>
<td>58**</td>
</tr>
<tr>
<td>Perceived legitimacy</td>
<td>686.5</td>
<td>498.5</td>
</tr>
<tr>
<td>Sense of empowerment</td>
<td>619.5</td>
<td>535</td>
</tr>
<tr>
<td>Total score</td>
<td>1058.5</td>
<td>161.5</td>
</tr>
</tbody>
</table>

* Wilcoxon Matched Pairs Signed Rank Test, two-tailed (Hassard, 1991)
** Statistically significant difference - critical value for the two-sided test at p value 0.05 is 446 (N=49).
These results show that only for the Knowledge domain is the smaller rank sum less than the critical value. This allows us to reject the null hypothesis at the 0.05 level of significance and conclude that counselling had a significant effect on the knowledge domain in study participants.

EFFECT OF MOTHERISK COUNSELLING ON DECISIONS CONCERNING MEDICATION USAGE INTENTIONS

The fourth objective of the study was also to show the nature and extent of the effect, if any, of the Motherisk Service on participants' medication taking; i.e., whether they took the same amount, less or more of the prescribed medication after counselling.

Upon learning of their pregnancy, 17 of 49 callers (35%) maintained their dosage level while 32 of 49 callers (65%) decreased their dosage level. Following counselling, 12 of 49 callers (24%) increased their dosage level, 32 of 49 callers (65%) kept their dosage level the same and 5 of 49 (10%) decreased their dosage level. A summary of callers' decisions concerning drug usage is shown in Figure 9.

Figure 9: Changes in medication usage post-counselling according to pre-counselling medication use.
However, after interviewing callers for the study it was clear that the advice and medication administration recommendations patients had received from their physicians sometimes changed upon the diagnosis of pregnancy and again over the course of the study. Between the diagnosis of pregnancy (pre-counselling) and post-counselling Motherisk interview, the participants' physicians endorsed, disagreed with or were neutral to their patients' decisions. The combination of physicians' advice and Motherisk information resulted in decision-making that was more complex and probably more confusing than anticipated. The outcomes are listed in Figure 10 below.

Figure 10: Changes in medication usage intention decisions pre- versus post- pregnancy according to physician advice received.

To help describe the feelings and experiences of Motherisk callers, two examples of common medication usage patterns in the study are outlined below.

1. One caller (040299) was told by her obstetrician to call Motherisk for advice but offered none of his/her own. After calling Motherisk the patient stopped her medication. She then called her family doctor who told her to stop the medication and that she would be monitored more closely. The symptoms of her medical condition returned in full force. Upon learning that she had stopped the drug her obstetrician became irate ("he
flipped") and told her to get back on her medication after which her symptoms improved.

2. Another caller (231198) continued to use her medication upon finding out that she was pregnant but consulted her physician, her pharmacist and the Internet. Her physician told her to call Motherisk, the pharmacist told her not to use the medication but didn’t check any literature ("off the top of his head") and the Internet source said that the risks outweighed the benefits. Her decision was to continue using the medication.

These cases give evidence of the confusing and contradictory advice that callers received or obtained. Regardless, callers repeatedly said that even though they may have been advised to stop a medication, the decision to not use the drug was strictly their own, not their doctor’s.

Stopping/reducing the medication resulted in either a return of symptoms, a worsening of the pre-pregnancy medical condition, self-described withdrawal symptoms, apparent withdrawal symptoms (based on descriptions), interruptions in daily activities, adverse effects on ability to work or no effect at all. (See Table 15) There was no association between adverse effects upon stopping a chronic medication and re-starting or increasing the dose again, using the Chi squared test.

Table 15: Callers with adverse effects upon stopping or reducing their dose of chronic medication and the association with increasing the dose again. (N=34)

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>7</th>
<th>17</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adverse effects</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total number</td>
<td>12</td>
<td>22</td>
<td>34</td>
</tr>
</tbody>
</table>

The calculated Chi squared value of 0.25 does not exceed the critical value of 3.84 (df=1) at a significance level of 0.05. Therefore the null hypothesis must be accepted.

Many women voiced the opinion that it was better not to take any drugs in pregnancy. Adverse outcomes from stopping medication were acceptable as long as they were still able to cope. One caller who was taking amitriptyline for fibromyalgia stopped her medication when she
learned that she was pregnant, on the advice of her doctor. Irregular sleep patterns developed over two days, worsened, then seemed to improve. After speaking with a Motherisk counsellor she did not restart the medication. She advised the counsellor that she would wait until her symptoms were a very serious health risk to her and her baby before re-starting.

Results also showed that the biggest impact on callers seemed to be from the first advice they received about taking their medication in pregnancy. As an example, one caller (210299) was advised in a previous pregnancy not to take her specific antidepressant. When she became pregnant she stopped. Her physician this time told her it was safe to use in pregnancy and strongly advised her to re-start but she refused, with resulting return of symptoms. She described herself as being depressed and a “mess”. After Motherisk counselling she still would not restart the drug and began avoiding going back to her doctor. Her sister who was a nurse also encouraged her to take her medication but the caller said that if something went wrong (with the pregnancy) she would still feel guilty - there would always be a doubt. This case illustrates the dilemma pregnant women experience and the impact of the first advice received.

At least two callers were able to switch to a “safer” drug in consultation with Motherisk and their doctor, even though the drug they were on was not considered to increase the risk of fetal malformations. “Safer” drugs, according to callers, were those that were on the market longer and that had been reported on more often in the literature.

To compare study participants’ use of prescription medication post- versus pre-counselling McNemar’s test (the paired Chi squared test) was used. Callers who were taking their chronic medication as before pregnancy (either as prescribed or less) were compared to callers who were not doing so. (See Table 16) These results showed that there was no association between Motherisk counselling and callers taking their medication post-counselling in the way they did before they became pregnant. Therefore, Motherisk counselling does not increase the probability that women who have decided not to take their drug as before pregnancy, will return to pre-pregnancy levels of drug usage post-counselling.
Table 16: Comparison of the effect of Motherisk counselling on women who are, and who are not, taking their medication as before pregnancy. (N=49)

<table>
<thead>
<tr>
<th>Pretest</th>
<th>Posttest*</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (8.0)</td>
<td>4 (9.0)</td>
</tr>
<tr>
<td>10 (15.0)</td>
<td>22 (17.0)</td>
</tr>
</tbody>
</table>

* McNemar’s test value of 1.79 does not exceed the critical value of 3.84 (df=1), p<0.05. Therefore the null hypothesis cannot be rejected.

Another pre-post comparison was made for callers who were taking their medication as prescribed or advised vs. those who were not doing so. (See Table 17) This latter group seemed less likely to be taking their medication as prescribed post-counselling because a proportion was not convinced of the value of taking their medication as prescribed even before they were pregnant. Pregnancy could either be an added deterrent to not taking medication as prescribed, but it could also serve as an incentive to maintain better health with appropriate medication dosing, than before pregnancy.

Table 17: Comparison of women who did, and did not, take their drug as prescribed pre-pregnancy. (N=49)

<table>
<thead>
<tr>
<th>Pretest</th>
<th>Posttest*</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (17.5)</td>
<td>10 (15.5)</td>
</tr>
<tr>
<td>3 (8.5)</td>
<td>13 (7.5)</td>
</tr>
</tbody>
</table>

* McNemar’s test value of 2.77 does not exceed the critical value of 3.84 (df=1), p<0.05.

These results showed that there was no association between Motherisk counselling and callers taking their medication as prescribed pre-pregnancy. Therefore, Motherisk counselling does not increase the probability that women who have decided to reduce their dose compared to before
pregnancy, will return to pre-pregnancy levels of drug usage. Again, there seems to be another factor involved in callers' decision on medication usage intentions.

Callers' physicians, in 11 cases, had advised their patients to stop taking or decrease the dose of the chronic medication targeted in this study, due to fears for the fetus' well being or development. Information that callers subsequently received from Motherisk might have refuted the basis for this advice but might not have been able to convince callers to continue taking their medication as prescribed before pregnancy. Therefore, a comparison of the effect of Motherisk counselling on callers who were taking their medication as prescribed or advised pre- and/or post-test and those who were not, is appropriate. (See Table 18)

Table 18: Comparison of the effect of Motherisk counselling on women who take their medication as prescribed/advised and those women who do not. (N=49)

<table>
<thead>
<tr>
<th></th>
<th>Pretest</th>
<th>Posttest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(6.9)</td>
<td>(17.1)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>(7.1)</td>
<td>(17.9)</td>
</tr>
</tbody>
</table>

* McNemar's test value of 8.1 exceeds the critical value of 3.84 (df=1), p<0.001.

Results showed that Motherisk counselling increased the probability that women who had chosen, on their own, not to take their medication as prescribed or advised precounselling, would take their drug as prescribed or advised post-counselling.

SUBGROUP EXPLORATORY ANALYSIS

The purpose of subgroup analyses was to determine what factors were associated with callers not taking their medication.

a) An exploration of the association between psychotropic medication and a decision to stop the medication.
There was no association, either pre-counselling or post-counselling, between stopping a medication and the type of medication used (psychotropic or non-psychotropic). (See Table 19)

Table 19: Association between type of medication (psychotropic vs. non-psychotropic) and the decision to stop the medication

<table>
<thead>
<tr>
<th></th>
<th>Psychotropic drug</th>
<th>Non-psychotropic drug</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>15</td>
<td>49</td>
</tr>
</tbody>
</table>

The calculated Chi squared value of 0.89 does not exceed the critical value of 3.84 (df=1) at a significance level of 0.05.

b) An exploration of the association between presence of a psychiatric condition and a decision to stop the medication.

There was no association between stopping a medication and whether a caller had a psychiatric condition or not either pre-counselling or post-counselling. (See Table 20)

Table 20: Association between presence of a psychiatric condition and the decision to stop the medication.

<table>
<thead>
<tr>
<th></th>
<th>Psychiatric condition</th>
<th>Non-psychiatric condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>15</td>
<td>49</td>
</tr>
</tbody>
</table>

The calculated Chi squared value of 0.37 does not exceed the critical value of 3.84 (df=1) at a significance level of 0.05.

c) Correlation between perceived legitimacy score and use of psychotropic medication.

There was no correlation (r = 0.12) between the perceived legitimacy score and a caller's use of a psychotropic medication.
d) Subgroup analysis of callers taking a psychotropic versus callers taking a non-psychotropic medication.

For callers taking psychotropic vs. non-psychotropic medication, none of the inter-group differences in domain scores, total scores, or change scores were statistically significant. However, there was trend towards those on psychotropic medication having a lower score in every domain, pre- and post-counselling, as well as having a smaller change score. (See Table 21)

Table 21: Domain totals for subgroups taking or not-taking a psychiatric medications.

<table>
<thead>
<tr>
<th></th>
<th>Taking Psychotropic</th>
<th>Not-Taking Psychotropic</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge pretest</td>
<td>9.5</td>
<td>10.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Knowledge post-test</td>
<td>14.5</td>
<td>15.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Knowledge change</td>
<td>5.0</td>
<td>5.3</td>
<td>0.79</td>
</tr>
<tr>
<td>Perceived legitimacy pretest</td>
<td>13.1</td>
<td>13.6</td>
<td>0.63</td>
</tr>
<tr>
<td>Perceived legitimacy post-test</td>
<td>13.0</td>
<td>14.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Perceived legitimacy change</td>
<td>-0.1</td>
<td>0.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Empowerment pretest</td>
<td>11.4</td>
<td>11.5</td>
<td>0.91</td>
</tr>
<tr>
<td>Empowerment post-test</td>
<td>11.3</td>
<td>11.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Empowerment change</td>
<td>-0.2</td>
<td>0.4</td>
<td>0.37</td>
</tr>
<tr>
<td>Total Score pretest</td>
<td>34.0</td>
<td>35.5</td>
<td>0.36</td>
</tr>
<tr>
<td>Total Score post-test</td>
<td>38.7</td>
<td>41.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Total Score change</td>
<td>4.7</td>
<td>6.5</td>
<td>0.40</td>
</tr>
</tbody>
</table>

MEDICATION USAGE QUALITATIVE RESULTS

Twenty-five callers were asked to answer the following question - did Motherisk counselling affect your decision to take medication in pregnancy. What was its value to you? Participants' responses had recurring themes that are summarized below.

In general, the Motherisk callers felt guilty and "paranoid" about taking a drug in pregnancy, especially during the first trimester. They talked about "holding out" for the first three months or
delaying re-starting their medication for as long as possible. Callers felt that society has made it forbidden to take drugs in pregnancy and that this idea has been “inbred” into them implying that taking a medication for a maternal condition would be self-serving. Women’s physicians often reinforced the previous feelings by voicing the same opinions, acting worried, showing concern about the woman having taken a drug or by being indecisive themselves.

1. Source of quality information.

Several callers did not think their doctors were giving them accurate or complete information. Some just simply did not want to take their doctor’s word on the matter especially if the doctor was unsure, provided sketchy or very little information, said they didn’t know a lot about drug risk or were unsure or simply said they didn’t know. Motherisk provided a “second opinion” which, at times, was also a source of confusion if other health professionals gave conflicting information.

2. Information provided relief, reassurance, and peace of mind.

Callers felt the information made them less concerned but not unconcerned and still mentioned some degree of fear. It gave them confidence in taking their medication.

3. Used information to support the decision that they may already have made.

Having already decided whether to take the drug or not, callers seemed to use the MR information to support or justify their decision. Some had already decided not to take the drug and said that MR didn’t provide enough information to change their minds. Others said that the information helped confirm their decision to take the drug, giving them confidence and helping them feel more at ease.

4. Information assisted caller in making her decision whether or not to take the drug.

A few callers said that MR assisted or helped them make a decision about whether or not to take the drug. Even fewer said that MR influenced their decisions. The main value of the information seemed to be in clarifying the risk.
Alternatively, many more callers said emphatically that Motherisk did not assist in their decision about taking their drug. They cited insufficient information as the main reason. When the drug had not been studied or reported widely, the lack of information helped many decide not to take the drug; callers seemed to be looking for a quantity of information. Many believed that there "should be something more", that there might be more information available that MR might just not have found. One woman was planning to do more research on her own. Callers wanted proof of safety and when this was not possible, they described Motherisk as providing mostly reassurance which wasn't what they were after.

Several callers pointed out that their decision to take a drug in pregnancy would be a personal decision, not their doctor's and not Motherisk's. They stated strongly that the information did not affect their decision to take or not take their medication.

5. The information about risk of fetal malformations gave callers a choice. It gave them freedom to choose among alternatives if that became necessary. They said they would use the information to support a decision they might need to make in the future.

Even though several callers were sure that they did not want to take the drug at this point in time (citing lack of need, improved medical condition etc.), they were grateful for the Motherisk information because it gave them the comfort and security in knowing that if their health was at risk, they could take drug. The information seemed to give them added resolve to try to stay off the drug knowing that they had an "out". They were convinced that the drug was relatively safe and that if they had to take it, everything would turn out alright.

A common belief among callers was that the duration of drug use was related to the risk of fetal malformation rather than whether it was taken at all.

6. Helped her switch to a drug with more studies, more information.

7. Assisted in decision of whether or not to terminate pregnancy.
Two callers had already scheduled an abortion, one because the pregnancy was unplanned but both changed their minds.

8. Used information to talk to their physician about choices and alternatives

**POWER CALCULATION**

The sample size needed for the study was recalculated based on the results obtained in the knowledge domain of the measurement instrument to determine if the study was sufficiently powered. The standard deviation ($\sigma$) of 3.84 and change score ($\Delta$) of 5.1 are listed in, and taken from, Table 13.

$$n = \frac{2(Z_{a} + Z_{b})^2 \sigma^2}{\Delta^2}$$

$$n = \frac{2(1.96 + 0.84)^2 \cdot (3.84)^2}{(5.1)^2}$$

$$n = 8.7$$

The same calculation based on the total score change of 5.3 and standard deviation of 6.79 resulted in a sample size calculation of 25. Therefore, this study was powered appropriately to find a difference if it existed but only for the knowledge domain. (Stolley et al, 1986) The instrument would require far too many patients to be practical to identify change in the other two domains.

**SATISFACTION SURVEY RESULTS**

The majority of Motherisk callers were satisfied with the service provided by Motherisk according to the results from the satisfaction survey of five questions (each scored on a Likert-type 5-point scale). (See Table 22) The mean score was 22.84 out of a possible 25. Only 9 out of 982 questions asked were given scores of 3 or less and the majority of these were in the process of information delivery. The qualitative responses from a question whether there were any comments about the service, matched the quantitative results.

Some callers admitted to questioning the authenticity and trustworthiness of the Motherisk service at first. One woman said she called three pharmacists for an opinion and all three reassured her that she could trust Motherisk. Following the Motherisk counselling experience,
however, callers were overwhelmingly positive and enthusiastic about their experience with the positive aspects far outweighing any negative aspects conveyed. They were extremely thankful that a service such as this exists and that more people should know about it.

Table 22: Summary of Results from the Satisfaction Survey (N=43)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Enough time</td>
<td>192</td>
<td>4.5 (2-5)</td>
</tr>
<tr>
<td>B. Treated with respect</td>
<td>204</td>
<td>4.7 (4-5)</td>
</tr>
<tr>
<td>C. Care about concerns</td>
<td>195</td>
<td>4.5 (2-5)</td>
</tr>
<tr>
<td>D. Convenient service</td>
<td>190</td>
<td>4.4 (2-5)</td>
</tr>
<tr>
<td>E. Satisfied with Service</td>
<td>201</td>
<td>4.7 (3-5)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>982</td>
<td>22.8 (17-25)</td>
</tr>
</tbody>
</table>

Motherisk callers gave the following reasons for assessing the Motherisk service as highly satisfactory.

- Confidential, caller anonymous
- There was a real human on the other end of the line
- Caring attitude of counsellors
- Current, reliable, substantiated and referenced information; quotes from the literature
- Available to the public and not just health professionals
- Unbiased information
- Reference paper provided
- Focused on her health as well, not just the baby's
- Good reputation, wonderful service
- An alternative source of information other than her doctor
- Left the decision up to the caller

The following were aspects of the Motherisk service that callers did not appreciate.
• Can’t share information with husband when delivered over the phone
• Information was perceived to be biased towards pro-life
• Counsellor took a position about drug use in pregnancy
• Counsellor talked too fast, too much information given too quickly- “the counsellor obviously knows it well and must have said it a million times before”
• Lines are too busy, takes too long to get through
• Unsure that information is correct, trustworthy
• Unsure of quality of information - number of patients, number of studies
• Advice was perceived as being geared towards the baby
• Phone message incorrect, didn’t match the experience

The following were suggestions by callers for improving the Motherisk Service.

• Send information by mail or FAX; callers would be willing to pay
• Internet site
• Longer hours past 9-5 slot, extended hours, weekend access
• Toll-free number
• Better access to clinic for callers from outside Metro Toronto
• Better advertisement of service, more information on MR itself
• More information, better studies
• Slower delivery of information; less automaton-sounding
• Visual information; if can’t see information, can’t understand
SECTION 4 - DISCUSSION

The study explored the effectiveness of the Motherisk medication-risk counselling service. A survey instrument was designed to detect changes in pregnant women callers' self-reported decisions about using a chronic medication in pregnancy. Callers were also assessed for their knowledge about whether their medication increased the risk of fetal malformations during pregnancy, how legitimate they perceived their medication use to be, and how empowered they felt in making medication-usage decisions. Interviews with subjects also provided information about what advice they had received from health professionals about their medication-use and whether they were satisfied with the Motherisk service.

This study also helped define and characterize the population of pregnant women who call Motherisk as well as the population of callers who take a chronic medication that does not increase the risk of fetal malformations.

Results (see Table 13) showed that Motherisk counselling had a positive effect only on the knowledge aspect of drug therapy self-management. Counselling alone did not significantly influence callers to continue or resume taking a prescribed medication for a chronic medication, during pregnancy. Pregnant women callers to Motherisk have a high sense of empowerment concerning personal drug use management and have a moderately strong perception that drug use in pregnancy is legitimate. Callers were highly satisfied with the Motherisk service but varied widely in how they used the information given.

SUBJECTS

Patients approached for this study were selected based on a systematic sampling approach. Each caller had an equal chance of being selected. As is evident in Table 2, the sample, compared to a representative group of all Motherisk callers, was similar with respect to
age, number of previous pregnancies, previous spontaneous or therapeutic abortions, and other characteristics that were not part of the inclusion criteria.

The sample was different in ways that would be expected according to the inclusion/exclusion criteria. More study participants had a fetus with gestational age in the first trimester, a chronic medical condition, more than one chronic medical condition, and been prescribed a non-teratogenic chronic medication. All study subjects had taken at least one of the medications they were asking about whereas almost half of all women calling Motherisk have not yet taken the drug(s) in question. Additionally, fewer women in the study sample called on their own or had called before; more were referred by their doctor. The latter might be explained by the fact that all had at least one chronic medical condition for which they were seeing a doctor.

There was also a disproportionate number of study subjects who were taking a psychotropic medication. This may have occurred because callers using psychotropic medications may have been less likely to receive risk advice from their prescribing physicians or because patients using psychotropics experience greater anxiety about the effects of their medications on the fetus. Additionally, callers using medications for other chronic conditions often require medications that increase the risk of fetal malformations (e.g., epilepsy, acne, rheumatoid arthritis) and thus would not have been eligible for the study.

The possibility exists that a greater representation from patients taking psychotropics might have resulted in an exaggerated number of patients choosing not to take their medication during pregnancy. Reasons for this concern are as follows. Compared to other chronic medications, psychotropic medications are frequently considered inessential or ineffective (Ruscher et al, 1997). Additionally there is a social stigma attached to taking this type of medication at any time but especially during pregnancy. However, a subgroup analysis found no statistically significant difference in medication usage decisions between subjects taking or not taking a psychotropic medication.

Results might have been different in callers from different cultural backgrounds as might be represented by women who did not speak English fluently enough to participate. In the experience
of Motherisk counsellors, callers tend to be fluent in English and this requirement did not prevent anyone from participating in this study. Results might also have been different if participants had been selected from a different setting such as an obstetrician's office or in cooperation with a pharmacy before the women had independently sought out risk counselling from Motherisk. In addition, non-callers might have provided different responses compared to women who called. Callers may already be highly motivated and empowered and have already made up their minds not to take their medication (as study results suggest) prior to calling Motherisk.

**PARTICIPATION RATE**

The participation rate in this study was 97%. Two potential subjects declined participation primarily due to time constraints. One patient was withdrawn from the study, three were lost to follow-up and four withdrew their consent. (See Figure 5) The dropout rate (12.5%) was slightly higher than a comparable, published study by Davis et al (1994) with a similar design. The latter study evaluated the impact of a rheumatoid arthritis patient education program on knowledge and self-efficacy and had a drop out rate of 8.9%.

The time between pre-test and post-test varied widely. This undesirable situation may have affected results because behaviours and attitudes naturally change over time as subjects experience new events and situations. (Nelson, 1980) However, persistence in calling participants back was important because studies have shown that callers who are easier to contact are different from callers who are more difficult to contact (requiring several phone calls over a period of time). (Streiner et al, 1995) Therefore, including all patients was likely as important as keeping the call-back time shorter.

Of the 49 callers to Motherisk, only one caller returned for a clinic visit. One possible reason for this low rate of return was that most callers lived outside the city of Toronto and would have had to travel some distance to attend clinic. In fact, only 10 (20%) callers were from the same area code as Motherisk. Sixteen (32.7%) were from the 905 area code in the Greater Toronto area. Twenty-three (46.9%) were calling long-distance from a total of nine area codes from six provinces. Another explanation for low clinic attendance might have been that callers were less anxious about
the risk of malformations because they were all taking a drug for which there was no increased risk of fetal malformation. Additionally, the majority of callers were very satisfied with the service or answers they received.

**INSTRUMENT VALIDITY**

In this study, the survey instrument was used to assess the effectiveness of Motherisk counselling. The instrument developed for this study was simple to use and easily administered over the phone. The three quantitative sections (hereafter referred to as the measurement instrument) could be tested for reliability and validity.

Test - retest correlation coefficients were within the range of 0.7 to 0.9 indicating that the test was reliable for at least the knowledge and perceived legitimacy domains. The high correlation coefficient for the Empowerment domain suggests that empowerment may be a relatively stable trait, that the questions may have been too similar or memorable or that the questions didn’t cover enough attributes of empowerment. (Streiner et al, 1995) For an evaluative survey instrument, the requirement for internal consistency is low. Nevertheless, the internal consistency, using Cronbach’s alpha, (Table 6) was within an acceptable range for the knowledge and perceived legitimacy domains, and low for sense of empowerment. The latter may have resulted from the inclusion of too few items (3 vs 4), or it may reflect the fact that the questions were measuring different attributes of a complex domain.

The coefficient of variation (Table 5) for all pretest and post-test scores was less than 1 indicating that the data were compact i.e., that there was a low variability about the mean. However, the coefficients of variation for the change scores were greater than 1.0 for the perceived legitimacy and empowerment domains; this may indicate a large between-patient difference. Reproducibility testing in stable patients (non-changers) (Table 7), defined as those who did not change the way they were taking their medication following Motherisk counselling, showed a change or trend to change in all domains. Therefore, the effect of Motherisk counselling on participants’ intention to take their chronic medication was not reproducible using the study measurement instrument, in the sample of stable participants. One interpretation of this result is
that the decision whether or not to take a medication in pregnancy is not an indication of a "stable" patient and that the measurement instrument may be more sensitive to actual change in callers than the "intention to take" question. Therefore for future reproducibility testing a more valid standard for defining changers and non-changers should be identified; if such a standard cannot be developed this method of assessing reproducibility should not be used.

In contrast, the within-person coefficient of variation (see Table 8) was low for stable patients meaning that results were reproducible for each individual patient. The different results of reproducibility testing suggest that when medication usage decisions are used as evidence of counselling effectiveness there are large between-patient differences in change scores. Moreover, different individuals making the same drug usage decision have different amounts of change. According to Streiner et al (1995) this characteristic of the population reduces the chance of an instrument being able to demonstrate overall treatment effects.

Responsiveness was high for the knowledge and empowerment dimensions as assessed by change in score in relation to change in the way the participant was taking her medication following Motherisk counselling (Tables 9 and 10) The knowledge domain was more responsive than the empowerment domain which in turn was more responsive than the perceived legitimacy domain. This means that more subjects would be required to be able to detect a change in the perceived legitimacy domain. Responsiveness as measured by effect size (Table 11) showed that the knowledge domain (effect size, 1.35) was very responsive under study conditions. According to a meta-analyses of effect studies, patient education usually has a substantial mean effect size of 0.49 (Kok et al, 1997); consequently this domain of the study measurement instrument performs comparably to other studies reported in the literature.

The survey instrument was theoretically based, the domains were chosen according to evidence in the scientific literature and endorsed by experts in the field, and the data generated from use of the instrument correlated well with comments received during interviews with Motherisk callers. Together these considerations support the instrument having content validity.
However, the model on which the survey instrument was based (see Figure 3) is complex and the factors hypothesized as determinants of drug therapy self-management are difficult to measure. The limited number of domains used narrowed the scope of the measurement instrument. Results could have been affected by items that were not measured by the instrument used in the study such as family support and physical environment. Additional domains such as self-efficacy and family/friend support should be added in future revisions to make it more comprehensive.

Construct validity was explored by measuring the correlation coefficient of divergent and convergent groups between the domain scores and medication usage intentions. Overall, the correlation coefficients were lower than expected. The highest correlation coefficients were found for the knowledge domain. The lowest correlation coefficients occurred with the empowerment domain. For example, there was no correlation between patients who called on their own and sense of empowerment. A likely explanation may be that the ability to refer oneself is a measure of self-efficacy rather than of empowerment. Evidence for the validity of the survey instrument was strengthened marginally by the results of the hypotheses testing. However, this type of testing is an ongoing process that should be repeated as the instrument is further revised and developed. (Streiner et al, 1995; Spilker, 1996)

Because study results showed that counselling had a variable effect on drug usage decisions and that providing risk information had a variable effect on domains other than knowledge, use of this patient population was not optimal to validate the instrument. In addition, quantitative and qualitative results showed that the relationship between any one domain and drug-use intention was complex. The theories on which the instrument was based support this finding. It is the interaction of all the domains, including ones not measured (self-efficacy, personal beliefs, environmental support), that would correlate best with drug usage decisions and not one of them on its own. Construct validity testing for the next expanded version of this instrument should be based on the test as a whole if the criterion for comparison or correlation is drug usage behaviour.

A homogeneous sample was selected to simplify the measurement of counselling effectiveness. However, this group was sub-optimal to assess instrument validity or
responsiveness because giving information over the phone had a limited impact on domains of DTSM other than knowledge. Additionally at baseline participants had moderately high levels of empowerment and perceived legitimacy compared to their level of knowledge, blunting the possibility of measuring an effect.

THE MOTHERISK SERVICE

Results showed that there was a statistically significant difference pre- and post- Motherisk counselling only in the knowledge domain. (Figure 6, Table 13, 14) Motherisk counselling unexpectedly had little effect on participants' perceived legitimacy and sense of empowerment scores. (Figures 7, 8)

Pre-counselling, participants scored lowest in the Knowledge domain, higher in the perceived legitimacy domain and highest in the empowerment domain. The possibility exists that any effect of Motherisk counselling on these domains as presented in the measurement instrument, would have been blunted in the sample population because the baseline level was so high the potential for change would have been much less. In contrast, the opportunity for seeing an impact would have been greatest in the Knowledge domain because the baseline was lower as well. This interpretation was supported by the linear correlation between the pre-counselling total score for each domain and the change in the total score post-counselling. The correlation coefficient was statistically significant for each domain. (Table 12)

According to Spilkert (1996), on a 7 point scale, a change of 0.5 in score in each category is a minimal clinically important different, a change of one is moderate and a change of 1.5 is large. Therefore, on a 5 point scale this corresponds to a score of 0.4 (minimal), 0.7 (moderate) and 1.1 (large). Therefore, the change of 1.0 in the knowledge score was a moderately large, clinically significant change. (Table 13) By these criteria, counselling did not result in clinically significant improvement in the perceived legitimacy score or the empowerment score.

Even though Motherisk counselling improved callers' knowledge, statistical testing showed no significant association between Motherisk counselling and callers resuming chronic drug use at pre-pregnancy levels. (Table 16)
Interviews with callers about the value of the Motherisk service showed that Motherisk counselling was valuable to them for many different reasons. (See Medication Usage Qualitative Results) While the same advice about “no added risk” was provided to each caller (in addition to evidence supporting lack of teratogenicity from the literature), callers interpreted the information differently. Some maintained it supported their decision to avoid re-starting their medication, some maintained it supported their decision to reduce the dose or stop their medication and some that it supported their continuing on the same dose.

In contrast, some callers were frustrated in their ability to use the information to make a medication usage decision. They insisted that they had made their medication usage decisions on their own and that Motherisk counselling had no measurable effect on their decision at all. In spite of this apparent lack of “value”, these same callers said that they were very satisfied with the Motherisk service. This apparent contradiction has been reported in the literature in similar circumstances. O’Connor et al (1998) compared the effect of a decision aid and information pamphlet on women’s decision to use hormonal replacement therapy in menopause. While the decision aid prepared women for making a decision by “creating realistic personal expectations, clarifying personal values, and supporting decision making….it had little effect on their decisions per se.” (O’Connor et al, 1998, pg 301) This observation also supports the theoretical model of relationships between elements in the DTSM model in that knowledge contributes to factors influencing drug therapy decisions but does not change it directly. (Bekker, 1999) (Figure 3)

Regarding drug usage decisions, the study showed that pregnancy seemed to polarize callers’ views on the value/risk of taking medication. (Figure 9) A majority of participants reduced or stopped their medication upon learning that they were pregnant, often on the advice of a physician (family doctor, obstetrician, specialist), pharmacist or therapist. Einarson et al (1998) also found that once callers had received negative information from a physician, it was difficult to convince them that the original information was incorrect. Once callers made the decision to stop or reduce their medication, their decision was hard to change even when they experienced adverse effects. Callers’ comments suggested that an ability to cope without medication in spite of adverse effects may have actually strengthened their resolve to stay off their medication. Therefore, it seemed as if
callers were following the first medical advice they received about taking their medication in pregnancy.

The possibility exists that for some reason callers were unable to use the information provided by Motherisk; many participants mentioned their frustration with the information given and their inability to use it to decide whether or not to take their medication. This behaviour may represent decisional conflict. According to Dobbins et al (1998) when evidence conflicts with previous advice/experience, fails to provide direction and therefore cannot be synthesized into the decision-making process, decision-makers tend to rely on gut instinct or intuition or alternatively they may fall back to a previous or currently held perspective or opinion. In some cases this leads to no decision being made at all. Therefore, for callers in this situation, it would be reasonable for them to continue using their chronic medication post-counselling as they had pre-counselling. One solution might be for Motherisk to place greater emphasis on delivering accurate medication risk information to women while they are planning their pregnancies i.e., earlier in the decision making process.

However, results did show that when Motherisk counselling was effective, it was greatest in callers who were independently choosing not to take their medication. (Table 18) Comments from participants showed that once participants received advice from their doctors about taking a medication in pregnancy, drug usage intentions following Motherisk counselling were less likely to change. The possibility exists that when women act on their own to stop their medication, without advice or direction from their physician, they are less sure of their decisions (less perceived legitimacy) and are therefore more receptive to Motherisk counselling. To determine if the pre-counselling perceived legitimacy scores differed between these two groups a t-test was performed comparing the group of callers independently choosing not to take their medication (perceived legitimacy - mean score 12.1) to the scores of the rest of the callers who were taking their medication as prescribed or advised (perceived legitimacy - mean score 14.3). There was a statistically significant difference (p=0.03) between groups; the difference supports the hypothesis that advice from health professionals increases the perceived legitimacy of taking a medication as prescribed or advised in pregnancy.
The literature also supports the finding that information alone does not change behaviour. (O'Connor et al, 1998; Bekker et al, 1999) A parallel can be found in studies examining the effect of information on physician's prescribing habits or medical practices. Kanouse et al (1995) describes the effect of information as "exceedingly modest". Durieux et al (1999) in a study of the effect of continuing medication on physicians' practices concluded that simple information diffusion may be one of the least effective methods of obtaining improvement. This evidence supports the Motherisk policy of offering a clinic visit to all patients on chronic medication in addition to telephone counselling even though, in this study, only one patient took advantage of this service.

The lack of association between the provision of information and drug-use behaviour suggests that the decision to use a chronic drug in pregnancy is complex and that confounding variables are involved. In fact, the Health Belief Model and Social Cognitive (Learning) Model would support this finding. It is likely that some factors, conditions or attributes included in the DTSM conceptual framework that were not assessed in this study (including self-efficacy, environmental concerns and personal attributes), were influencing drug usage intention decisions. Alternatively, results from the study suggest that some adjustments should be made to the conceptual model developed in Figure 3. Personal beliefs and environment should be positioned to show that they are factors affecting empowerment, perceived legitimacy and self-efficacy and are clearly not influenced directly by knowledge. (See Figure 11)

Essentially all study participants were highly satisfied with the Motherisk service. (Table 22) To prevent callers from feeling awkward, the satisfaction survey was given after the post-test by an investigator who was not employed by Motherisk and who did not provide the risk-assessment information. The majority reported that Motherisk gave them "peace of mind" and helped relieve a sense of guilt. It may be that the knowledge provided increased their confidence in making a decision or provided confirmation for a decision already made even though it didn't change their decision. Even the act of accessing Motherisk allows pregnant women with chronic conditions to assert some control over their illness; it fulfills their role as managers of their own drug therapy. This type of outcome has been described in the literature as a "mental" outcome rather than a physical outcome. When Sherbourne et al (1999) asked patients what outcomes mattered most to them,
they valued mental and social outcomes nearly as much as physical health outcomes. It is plausible that the “added value” of Motherisk counselling is the niche it fills in providing mental support to chronic medication users in pregnancy that is not always available through routine prenatal care that focuses primarily on physical outcomes.

\[\text{Figure 11 - Revised conceptual model of medication use decision process.}\]

Post-counselling interviews and survey instrument results supported the impression that Motherisk callers are women who already feel empowered in managing their drug therapy. (Figure 8) Callers did not appear to accept the concept of “no increased risk” but rather seemed to decide
that such an absolute did not exist and independently assessed "no increased risk" medications along a continuum from less risky to more risky anyway. (See Medication Usage Qualitative Results) An unexpected finding was the extent to which callers did not accept the Motherisk information at face value. Comments showed that callers assessed the quality, accuracy, thoroughness and reliability of information they received regardless of the quality of the counselling. They also sought out many sources of information and discussed the Motherisk counselling with their doctors.

The subgroup analysis of subjects either taking or not taking a psychotropic medication and having or not having a psychiatric condition (Tables 19, 20), showed that there was no statistically significant difference in drug usage intentions. Additionally, pre- and post-counselling scores for each domain and each domain change were compared, and again there was no statistically significant difference. There was, however, a trend in callers on psychotropic medication towards having a lower score in every domain, pre- and post-counselling as well as having a smaller change score. This trend was most noticeable in the perceived legitimacy domain. (Table 21) There is evidence in the literature to support this observation. According to Ruscher et al (1997), a large percentage of psychiatric patients oppose taking medication on principle and generally believe that medication isn't effective. Even though Motherisk counselling did not significantly affect this domain, the low perceived legitimacy score obtained by participants lends support to the validity of the perceived legitimacy domain of the study instrument in measuring what it was supposed to measure.

**INTERNAL VALIDITY**

A non-randomized, one-group pretest-posttest design cannot be used to make "unequivocal causal inferences" because there is no comparison group. (Barker et al, 1994) The design is suitable for collecting data on mediating or moderating variables and to explore associations and correlations. For the purposes of an exploratory study, the design was appropriate.
Another design that could have been used is the non-equivalent groups pretest-posttest design in which one group of callers would receive the pre-test and post-test with counselling while another comparable group would take both tests but not receive any counselling. However, Motherisk is available throughout Ontario and finding women unaware of the service, to make up the control group, would have been difficult. Once recruited for the study, the control group would have become aware of the service and then it would not have been ethical to withhold risk information for the required time between pre- and post-test as it may have caused unnecessary anxiety. In addition, the possibility exists that Motherisk callers are different from women who don’t call; better educated and more informed of health care issues. Therefore, it could be argued that using a control group would not have been appropriate.

A randomized experimental design would allow manipulation of a single variable to help establish cause and effect but there were two major problems. An appropriate outcome measure (ie. Survey instrument) had not been developed. Finally, until the important variables have been identified, an experimental, randomized study can not be properly designed.

Therefore, this pre-test, post-test design was justified because the purpose of the study was to test a new site-specific survey instrument and to describe the beliefs and attitudes of a specific population i.e. Motherisk callers. It was also exploratory because the effect of risk information and counselling on DTSM is poorly understood.

The changes identified following counselling could have occurred on their own by chance or as a maturational trend. The results could have been a reaction of callers to having their attitudes/beliefs questioned. The time period between the pretest and posttest would have allowed for intervening events to exert their influence on callers as well. However, according to the results and re-calculation of the sample size, the design was sensitive enough to identify a clinical change when a change occurred.

The counselling situation for the pre-test and post-test were different. The post-test investigator was less experienced in risk counselling and was not under the same time-constraints
that the pre-test counsellors had. The different approach may have influenced callers' responses in an unpredictable way.

Even if we accept that Motherisk effects a change in callers' attitudes we also need to be aware of threats to the construct validity (Barker et al, 1994). Some of these include: confounding variables, expectancy effects (related to placebo effect), Hawthorne effect (introduction of any new procedure produces a beneficial change). In considering the Hawthorne effect in this study there is a chance that the survey instrument itself produced a beneficial change. For example, the extra time and attention given to the caller during the counselling interview might somehow have changed the Motherisk message or given it more credibility. One way of exploring the Hawthorne effect would be to compare the post-test of the study group to a post-test of another group who received the Motherisk intervention but did not take the pre-test. (Barker et al, 1994)

**GENERAL DISCUSSION**

The project was significant in that it provided insight into the impact of Motherisk counselling on decision-making behaviour concerning medication usage intentions in pregnancy. The implications for practice situations are as follows. If a physician's advice or the first medical advice received is important in influencing medication usage decisions it is important to provide accurate risk-assessment information to physicians looking after pregnant women. The liaison of Motherisk and other risk-counselling services with the medical community is of vital importance. Consistency among health professionals is also essential to avoid confusing callers and to avoid creating decisional confusion; therefore all health professionals in contact with pregnant women should be educated appropriately concerning the risks of taking medication in pregnancy. The multidisciplinary approach of Motherisk is in line with this recommendation.

Because the impact of risk-assessment information dissemination is limited, if an effect on DTSM or drug compliance is desired, innovative methods of delivering information should be sought. Possibilities include the use of a decision aid (O'Connor 1998), pre-recorded messages, or an Internet Web Site where information can be retrieved, risk explained or the authenticity of Motherisk show-cased. Research in this area may help define the role and value of patient drug
information and suggest ways of optimizing counselling to improve effectiveness. For example, studies have shown that the involvement of relatives is important. Mantonkis et al (1985) showed that the prejudice of relatives against using drug therapy in schizophrenics correlated with a negative attitude toward drug therapy by the patient. Perhaps the same prejudice against drug use in pregnant women occurs in Canada. Finally, in consideration of other factors that influence women's DTSM, Motherisk might explore ways or techniques to improve patient self-efficacy.

Women do not appear to understand the concept of risk and are looking for black and white answers. They want guarantees of safety. In addition, they do not always appear to accept or understand the role of non-medical professionals in providing health-related advice. Callers may be more accepting of Motherisk statements if they were given a brief explanation of what risk is, what science can accomplish through research, and what can reasonably be expected from a risk-counselling service. To better understand their needs, a question such as, “What would convince you that this drug was safe in pregnancy?” would be interesting to ask. For women who cannot understand why Motherisk may have more current information than their physicians, it would be helpful to briefly explain how the statements are researched and what the role of non-medical professionals is in supporting the physician in our health care system.

Society has a bias towards not taking drugs in pregnancy. The benefits of taking a drug in pregnancy can be overwhelmed by highly publicized outcomes of fetal malformations. The latter is more familiar to women, simpler to understand, and easily imagined within a personal context. (Fischhoff et al, 1980) To ensure women receive balanced information to make possible better DTSM decisions, the benefits of medication and disease knowledge and treatment, must also be presented. Only physicians and perhaps pharmacists, who have access to the patient's medical information, are in the position to fill this gap. Future research might also explore the effect of risk counselling on how women interact with or relate to their physicians for the rest of the pregnancy. Perhaps patients of physicians who are ready for shared decision-making, would be more receptive to counselling.
To enhance understandability of the Motherisk population's decisions concerning chronic medication use, future research should study the impact of counselling on other domains of DTSM namely self-efficacy and perception of support. Study results also suggested outcomes that might be used in pharmacoeconomic studies such as time lost from work due to recurrent illness following medication stoppage, numbers of consultations with health care professionals or health care usage. In the future we might want to see if callers with a higher DTSM score are more satisfied with their total health care or if they have better pregnancy outcomes. Alternatively it would be interesting to see what decisions callers make in a future pregnancy or to compare the percentage of women callers planning a pregnancy now versus two years ago.

The use of a reliable instrument to measure DTSM is essential. The instrument developed for this study could be used in other TIS to evaluate the effectiveness of risk counselling. In the future, the instrument could be used to identify domains of DTSM in which the caller has lower scores thereby allowing counselling and support to be targeted. Because a relatively homogeneous population was needed to reduce variance, for adequate statistical power, the results may have less external validity, i.e. generalizability. One option to increase generalizability would be to repeat the study in a different population or with a different intervention. (Barker et al, 1994)

This study assessed the effectiveness of Motherisk counselling on DTSM, specifically on knowledge, perceived legitimacy, personal empowerment and drug-usage decisions. These have been called process variables. Research in this area is important to determine what variables are affected by counselling so that methods for improvement can be suggested. However, good decisions do not equal good outcomes. (O'Connor, 1998) According to Entwistle et al (1998), health outcomes should be used in evaluating an intervention in a health care system attempting to improve health status. Therefore, the next step in measuring the effectiveness of risk-counselling would be to measure its effect on health status and well-being, currently and in the long term.
CONCLUSIONS

The conclusions that can be drawn from the study include the following:

1. Motherisk counselling increased the knowledge of callers about the risk of malformations from medication use in pregnancy.

2. The value and usefulness of Motherisk information varied greatly between callers and contributed differently to their medication usage decisions.

3. The majority of callers reduced or stopped their medication use before calling Motherisk. Improving callers' knowledge about the lack of increased risk of fetal malformations upon taking a chronic medication during pregnancy, did not restore their medication use to levels before pregnancy.

4. Callers who had independently decided not to take their medication as prescribed upon learning that they were pregnant were most influenced by Motherisk counselling to return to their pre-pregnancy dosage level.

5. Motherisk assists pregnant women in fulfilling their role as managers of their own drug therapy in partnership with health professionals. This allows these same women to assert some control over their illness and contributes to their peace of mind during pregnancy. This benefit/outcome of service can be justified as mental/social support and its importance should not be trivialized.

6. Callers are discriminative consumers. They did not accept Motherisk information at face value but assessed its quality, accuracy, thoroughness, and reliability regardless of the quality of counselling.

7. Decision-making about medication use in pregnancy is extremely complex. To help women avoid decisional conflict, counselling/information about medication risk during
pregnancy should be provided as early as possible preferably before pregnancy even occurs.

8. Motherisk callers tended to follow the first professional advice, about the risk of fetal malformation from medication taken during pregnancy, that they received.

RECOMMENDATIONS

MOTHERISK SERVICE

Given the high expectations of callers, the primary goal of Motherisk must be to maintain both a high quality of service (qualified counsellors, increased accessibility) and a high quality of information. Accurate and consistent information is important to improve public confidence in the information provided. Motherisk should explore creative ways and formats of providing information to meet the needs of more callers but at the same time address the needs of counsellors who cannot be expected to repeat the same information over and over again and remain enthusiastic. Innovative ways to counsel patients and their families should be sought, studied and improved. To assist callers in interpreting the information, they should be educated about what risk is and about how Motherisk operates within the healthcare system.

The service should be better advertised to health professionals across Canada. Callers from areas outside Toronto are disadvantaged because they cannot easily attend clinic. An outreach program or guideline could be developed to support physicians in remote communities in providing risk counselling in their office. Additionally, callers should be provided with more information about the Motherisk service itself; its authenticity, funding, staffing, resources and status within the healthcare community to help improve their confidence in the information provided.

A special challenge to Motherisk is women who have been given incorrect risk information by their physician, pharmacist, therapist or any other health professional. This group of callers should be identified during the Motherisk interview. More time or resources should be directed to them. Motherisk should educate physicians and other health professionals about the service and about risk-counselling for medication use in pregnancy.
FURTHER RESEARCH AND SUGGESTED ALTERATIONS TO IMPROVE THE STUDY

The most important way that this study could have been improved would have been to have a comparison group such as women who received information on medication with an increased teratogenic risk or women attending a prenatal clinic who had not called Motherisk. The latter group could have been pre-tested with the survey instrument, referred to Motherisk then post-tested afterward. In addition to making the results more meaningful, a comparative study would have facilitated validation of the survey instrument.

Further research into medication usage behaviour or the effects of Motherisk should include women at all stages of pregnancy and those in the planning stages. The original study was planned to survey women in the first trimester to assess the effect of counselling on plans to terminate a pregnancy due to fears of fetal malformation from a chronic drug. However, by excluding this particular question, the survey would have been relevant to women at all stages of pregnancy. In addition, making the survey instrument more generic to any type of counselling in pregnancy would make results more generalizable and usable outside the Motherisk service.

The survey instrument should have had more domains representative of DTSM (e.g., self-efficacy, environmental influences, personal values) even though Motherisk counselling alone would have been unlikely to have influenced them. This might have been accomplished by having more patient input into the questions. The value of patient qualitative interviews should not be underestimated. For example, to obtain a greater understanding of the decision-making process before preparing the DTSM instrument, it would have been interesting to ask callers, "what would it take to change your mind about taking your medication during pregnancy", or "what would convince you that a drug is safe in pregnancy".

With respect to the DTSM measurement instrument, the empowerment domain should have had at least one more question to cover more dimensions. One possibility would be a question about past behaviour such as, "Have you spoken with your doctor about the importance of taking this medication during pregnancy." The knowledge domain would also have benefited from the addition of a question about "enough" information such as, "Do you have enough information on..."
which to base a decision about whether or not to take this drug in pregnancy?" A domain on
decision making that includes decisional conflict and decisional confusion would be important to
capture given the answers to the question about the value of the Motherisk service. The element of
certainty of or confidence in the decision already made would be insightful. (Lorig K et al, 1989) To
improve the satisfaction survey in the future, a question about how balanced the information was,
would have been helpful.

Results from the study showed that actual medication usage is not a fair or valid outcome
measure of Motherisk counselling. In future research valid outcomes should include service
satisfaction, DTSM or effect on medication usage decision-making.
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APPENDIX 1 – Motherisk Background Information

Half of pregnancies in North America are unplanned, therefore, fetal exposure to virtually any drug will be inevitable. Following exposure to drugs, chemicals or radiation, women have traditionally relied on their physicians and on the media (books, magazines and television) for answers regarding the risk to their fetus. Unfortunately, the literature available to the primary care physician is often conflicting, inadequate and subject to change. Drugs are often marketed with a warning of unproven safety in pregnancy. (Koren et al, 1993; Koren et al, 1986) Therefore, most women are at risk of receiving incorrect and/or exaggerated information about fetal risk following maternal exposure. (Bentur et al, 1991) This may lead to women being exposed unknowingly to a teratogen during pregnancy. Alternatively, the perception of risk may lead to unnecessary anxiety during pregnancy and at times, to unnecessary pregnancy terminations. (Koren et al, 1989; Koren et al, 1990)

In response to these needs as well as legal pressures, teratogen information services (TIS) such as Motherisk at the Hospital for Sick Children in Toronto, were created. Their primary job has been to interpret information regarding known and potential reproductive risks from various maternal exposures into risk assessments for the developing fetus. Most TIS have an information and consultation service to assist the pregnant woman and her physician in understanding fetal risk(s) that may be associated with exposures in pregnancy. With this information, the pregnant woman can hopefully make more informed decisions during her pregnancy with respect to either continuation or termination.

Objectives: The objectives of the Motherisk service are: 1) to provide authoritative information to assist pregnant women and their physicians in understanding the fetal risk associated with an exposure during pregnancy. 2) To develop and maintain an active educational and research program in the area of reproductive and developmental toxicology at the
undergraduate, graduate and postgraduate levels. The research program addresses unanswered questions on safety of drugs, chemicals and radiation during pregnancy and lactation. (Koren et al, 1993)

Program Description: Motherisk is a hospital-based telephone service available to health professionals and to the general public. Incoming calls are received by information specialists, who decide whether the caller should be referred for a clinic appointment or to the physician on call or whether the query is such that the information specialist may answer the call satisfactorily. Of the approximately 1200 telephone queries received per month, 10-15% of callers are scheduled for a clinic appointment and counseled by a physician affiliated with Motherisk.

All patients attending clinic rate their perceived level of risk of delivering a baby with fetal malformations using a visual analog scale (VAS) prior to and following a counselling session. During counselling, patients are provided with information on the risks of exposure-associated fetal malformations.

Follow-up of pregnancy outcome is performed in all cases in which women are consulted in the clinic and in selected cases of telephone contact only. Telephone follow-up is conducted by an information specialist or a pharmacology/toxicology undergraduate student affiliated with Motherisk, approximately 12 months after the expected birth of the offspring. During the interview, data is collected about additional exposures in pregnancy, maternal health during pregnancy, delivery information and neonatal health and developmental milestone acquisition. A separate form is sent to the child's physician who corroborates the information gathered during the interview. All incoming data are stored in a database and are subsequently used to generate new data on the safety of drugs and chemicals in pregnancy. (Motherisk Fact Sheet)

99
APPENDIX 2 – Structured Qualitative Interviews

Structured Qualitative Interviews with Motherisk Clinic Patients
August 7, 1998

Questions Asked: (Not all questions were asked or asked in this order. A lot depended on how responsive the patient was and how they answered the first question. Those who said they followed their physician’s directions perfectly were the most non-responsive to even thinking about considering the questions or forming an opinion.)

- are you pregnant now
- how do you normally take medication
  - do you take it exactly as prescribed
  - do you ever take more or less
  - do you every adjust the amount you take according to how you feel
- what do you think about taking medications in pregnancy
  - is it safe to take any drug
  - any concerns
  - if a medication increased the risk of a birth defect, how much of an increase would there need to be before you would stop taking it
  - if you don’t take a medication during pregnancy that you would normally need, would you be concerned about your health
  - if you wanted to decrease the risk of a medication on your baby, what might you do
- what type of information do you want to know about a medication when you’re pregnant
- where do you get information about medications in general (prompt - friends, books, doctor, family, nurse, pharmacist...)
- how much confidence do you have in the information?
- do you trust the information from all sources equally?
- what makes some information more trustworthy than others? (e.g. a professional giving it, amount of info, if it is written etc....)
- how does the information you received at MR compare to what you may have gotten elsewhere?
  - what led you to that decision
- once you have the information you need, do you feel you have the right to decide whether to take it or not
- do you think patients should always follow their doctor’s directions regarding taking drugs
IN GENERAL:

- not many had received enough information to decide whether it was trustworthy
- if the patient’s doctor was supportive and there seemed to be a good relationship between them, the patient seemed more willing to say she took her drugs as prescribed without undue anxiety
- one patient was indignant that someone might think she wouldn’t do as she was told by her doctor

Patient #1

She was concerned about getting information on the risks of taking drugs in pregnancy and what she could do to decrease the risk. She said it was easy to take drugs as prescribed and normally takes them as directed by the doctor. Her doctor is generally supportive and told her that if she didn’t take her medications that she would end up in the hospital and she believed him. Her family and friends are supportive of her taking medications during pregnancy. She has had a good experience with Motherisk in the past and attended the MR clinic during a previous pregnancy. She is still worried about the effects of the drug on the fetus. Apparently her daughter has seizures and she thinks that taking prescription medication during that pregnancy contributed to that condition. Regardless, she believes that she absolutely had to take medication for her own health in spite of any possible effects on the baby.

Patient #2

This patient thought that a 20-25% teratogenic risk would be a range where she would become concerned. She thought that a risk of 5% was not significant. She said she takes her medications exactly as prescribed and follows the directions precisely. However, she sees her doctor as an advisor and thinks that the decision whether to take medication is hers, ultimately. She didn’t think she needed any more information about the effects of her medication in pregnancy and doesn’t need anyone’s help or support in taking her medication properly. She gets the information she needs from a nurse at the clinic she goes to. However, to decrease the risk of a teratogenic effect from a drug, she would not take it during the first trimester.

Patient #3

This patient was not taking any medication at this time for a chronic condition in pregnancy. She was concerned about an infectious contact. Normally she takes medication exactly as prescribed and doesn’t miss doses. She would not take more or less but she would decide either to take it or not to take it. She thought she was the ultimate decision maker when it came to drug-taking. She thought the information from her doctor, specialists and information pamphlets (in the doctor’s office or elsewhere) was trustworthy and she takes it into consideration when making medication use decisions. She doesn’t believe or trust information from her friends or family although her family often helps her make medication decisions. Any teratogenic risk more than 1-3% was too much risk for her. She wouldn’t take any medication if it increased the risk at all above this amount. Overall she hasn’t given a lot of thought about taking medications in pregnancy and believes that doctors should know if they are safe or not. She believes her doctor is the expert.

Patient #4

Patient #4 is not pregnant but is in the process of deciding to. Overall she hasn’t thought a lot about medication and pregnancy. She thinks she needs her medication and if it is too risky then she would choose not to become pregnant. She occasionally adjusts the medication dose according to how she is responding or feeling. A risk of more than 6 to 10% would be too high and would convince her not to become pregnant. She feels that her health is important to the baby’s
health. She believes there is a safe dose in pregnancy - it is not an all or none phenomenon. The type of information she thinks is useful for making medication decisions is risk assessment and safe dosing. She gets her information about drug use in pregnancy from her family doctor and health pamphlets and trusts both equally. She thinks she has a right to decide whether or not to take a medication.

Patient #5

This patient was pregnant and was not taking a medication for a chronic condition. She takes her medication as prescribed for now but thinks she might take less in certain cases. She doesn’t know if drugs are safe in pregnancy but thinks it depends on the illness or medical condition that the mother has. Her own health is as important as that of her fetus in her opinion. She said that the concept of risk is difficult to understand. Using the words low, medium or high risk would be more comprehensible than a percent increase or overall percentage. She knows her doctor well and trusts his opinion over everyone else’s. After his opinion, she would trust Motherisk counselors. She doesn’t think the advice of family or friends is reliable although she does take information back to them for discussion. The type of information she would like about medication in pregnancy is the type of birth defects the drug could cause. Whether the defect would be physical or mental was important. She thinks that scientific studies are the type of information that is trustworthy. She thinks she has the right to decide ultimately whether to take a medication in pregnancy although if a doctor said to take it, she would.

Patient #6

This patient said she wants to take her medication exactly as prescribed, no more or less although she occasionally misses a dose. She doesn’t like medication at all and is concerned even more about taking any in pregnancy. Mostly she is concerned about birth defects. She is taking medication to prevent seizures and felt that her health was equally important to that of the fetus. She believed that if she had a seizure it would hurt the baby too. The risk of a birth defect would have to be more than 8-10% before she wouldn’t take a medication in pregnancy. She thinks that it is ultimately the doctor’s decision about whether she should take a drug in pregnancy or not. She trusts doctors and pharmacy inserts. She does not get a lot of information from her family or friends. She “sort of” understands the information she has been given and thinks there is a safe way to take a medication in pregnancy. When asked how medication taking could be made safer in pregnancy she said that it might be safer to take less - the doctor should be able to tell her how to make it safer.
APPENDIX 3 – Sample Data Collection Form
PILOT STUDY: ASSESSMENT OF THE EFFECTS OF RISK-COUNSELING (MOTHERISK) ON PRESCRIPTION MEDICATION SELF-MANAGEMENT PRACTICES. - Data Collection Form

Motherisk Number: ______________________

Date: ____________________ Patient Name: ______________________

Complete the Motherisk Intake Form up to collection of current medication and review to see if Patient meets inclusion & exclusion criteria. MEETS INCLUSION CRITERIA? _______ YES

Prescribed Medication (for study purposes):

Medical Condition (for study purposes):

STUDY PARTICIPATION INTEREST:

If they’ve called before - say I know you’ve called before but we are currently doing a study where we ask callers to answer a short questionnaire about how they take medications during pregnancy and their thoughts, beliefs and feelings about it. It would take about 3 minutes of your time if usual today, then we’d like to call you back in about a week and ask you a few other questions that will again take about 2 to 3 minutes. Would you be interested in participating?

New callers - Before we go any further I’d like to tell you about a research study we’re doing here at Motherisk to help improve our service. We’d like to ask you to answer a short questionnaire about how you take medication during pregnancy and your thoughts, beliefs and feelings about it. It’ll take about 3 minutes more of your time today then we’d like to call you back in about a week and ask you a few other questions that will again take about 2 to 3 minutes. Would you be interested in participating?

______ YES _______ NO (proceed with counselling)

Can someone call you back at the number you gave me before? ___ yes
If no, where can you be reached in about 3 to 5 days?

______ business? OR home? (circle)

What is the best time to call? ______________________
Other comments: ______________________

Informed Consent:

The questions I’m going to ask you may make you think about ideas or concerns you’ll want to discuss with your doctor, family or friends. If you don’t want to answer a certain question, just tell me you don’t wish to answer it. You don’t have to give me a reason. You are free to stop this interview at any time and you will then be given the same counseling information that any caller to Motherisk receives.

All your answers will be kept confidential and will be seen only by me or Motherisk staff. After we call you back in about a week, I’ll be taking your name off any records. If the study is published, you’ll be identified by a number only.

Any questions? Consent given? ______ yes ______ no (if no proceed with counselling)

COMMENTS: ______________________

104
PRE-COUNSELLING TRANSCRIPT:

I'll begin the questionnaire now. (Have patient think of one drug in particular.)

Has anyone given you advice about taking (medication) in pregnancy?
Who? (could be more than one person e.g. friend, doctor etc.)
1. ___________________________________ 2. ___________________________________ 3. ___________________________________ 4. ___________________________________

Have you read or heard any general advice about taking your type of medication during pregnancy? If yes, what was the source?
5. ___________________________________ 6. ___________________________________ 7. ___________________________________

Now I'm going to be reading several statements and after each one, I would like you to think about how much you agree or disagree with it.
1 means you strongly disagree, 2 means you disagree, 3 means you are unsure, 4 means you agree and 5 means you strongly agree. Should I repeat that? Here we go.

KNOWLEDGE - COGNITIVE APPRAISAL.

<table>
<thead>
<tr>
<th>Number 1-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Taking (medication) during pregnancy will NOT increase the chances of birth defects.</td>
</tr>
<tr>
<td>b. Right now, I have enough information about (medication) to decide if it's safe to use in pregnancy.</td>
</tr>
<tr>
<td>c. I understand the information I have about (medication) during pregnancy.</td>
</tr>
<tr>
<td>d. I trust the advice I have already received about taking (medication) during pregnancy. (ask for each person/source of advice from above)</td>
</tr>
</tbody>
</table>

#1: ____________________________________
#2: ____________________________________
#3: ____________________________________
#4: ____________________________________
#5: ____________________________________
#6: ____________________________________
#7: ____________________________________

PERCEIVED LEGITIMACY OF DRUG USE DURING PREGNANCY

<table>
<thead>
<tr>
<th>Number 1-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Before becoming pregnant, I was satisfied with (medication) as a treatment for (medical condition).</td>
</tr>
<tr>
<td>b. Now that I am pregnant, I am satisfied with (medication) as a treatment for (condition).</td>
</tr>
<tr>
<td>c. To stay healthy during this pregnancy, it's important for me to take (medication).</td>
</tr>
<tr>
<td>d. To keep the baby healthy during pregnancy, I need to keep myself healthy by taking (medication).</td>
</tr>
</tbody>
</table>

105
Motherisk Number: ________________________

1 = strongly disagree, 2 = disagree, 3 = unsure, 4 = agree, 5 = strongly agree

**SENSE OF EMPOWERMENT**

<table>
<thead>
<tr>
<th>Number 1-5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. During pregnancy, I have the right to decide whether or not to take (medication).</td>
<td></td>
</tr>
<tr>
<td>b. During pregnancy, I have the right to decide how much (medication) I'm going to take even if it's different from what my doctor prescribed (during pregnancy).</td>
<td></td>
</tr>
<tr>
<td>c. I have the right to question my doctor about the safety of taking (medication) during my pregnancy.</td>
<td></td>
</tr>
</tbody>
</table>

**MEDICATION USAGE**

→ Now I have a few questions about the way you take medication. Before becoming pregnant, were you taking [medication] exactly as recommended by your doctor? _______yes _______no

If no, were you taking more _______ (check) or less _______ (check)?
How much (more or less)? ________________________________

→ Since becoming pregnant, have you changed the way you are taking [medication]? _______yes _______no

(If yes): Are you taking more _______ (check) or less _______ (check)?
How much (more or less)? ________________________________

(If yes): Was this change recommended by anyone? _______yes _______no

(If yes): Can you tell me who? _______doctor _______partner _______pharmacist _______nurse _______friend Other: (specify) ________________________________

(If yes): How do you think this has affected your health?

___ daily activities (explain) ________________________________
___ diet (explain) ________________________________
___ sleep patterns (explain) ________________________________
___ medical condition (explain) ________________________________

→ For patients offered a clinic appointment please complete below:
Clinic appointment planned? _______yes _______no  If yes, clinic date/time: ________________________________

Just a reminder that another counsellor will be calling you again in about 3-5 days.

Counsellor: ____ Michael ___ Samar ___ Adrienne
POST-COUNSELLING TRANSCRIPT:

"Good morning/afternoon/evening. Is Ms X available please? [If not available, the following message will be left.] Please ask her to call ______ at ______

[If Ms X answers, proceed as follows]

"Hello. This is ______ calling. A counsellor at Motherisk spoke with you last ______ when you called the Motherisk Department at the HSC. At that time you participated in a study and agreed that I could call you back with a few more questions. Would you be willing to answer some questions now? Is this a convenient time?"

[If it is a convenient time, proceed with the instructions and questions as per Part A, but replacing the pre-counselling questions with the post-counselling questions. If it is not a convenient time, then inquire what time will be convenient, and call back. Read the "participation" section of the informed consent page to remind the caller about her rights to withdraw consent or to choose to answer questions.]

1 = strongly disagree, 2 = disagree, 3 = unsure, 4 = agree, 5 = strongly agree

POST-COUNSELLING QUESTIONNAIRE

KNOWLEDGE + COGNITIVE APPRAISAL

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PERCEIVED LEGITIMACY OF DRUG USE DURING PREGNANCY

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1 = strongly disagree, 2 = disagree, 3 = unsure, 4 = agree, 5 = strongly agree
PILOT STUDY: ASSESSMENT OF THE EFFECTS OF RISK-COUNSELLING (MOTHERISK) ON PRESCRIPTION MEDICATION SELF-MANAGEMENT PRACTICES. – Data Collection Form

Motherisk Number: ________________________________

SENSE OF EMPOWERMENT

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</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td><strong>b.</strong> During pregnancy, I have the right to decide how much (medication) I’m going to take even if it’s different from what my doctor prescribed (during pregnancy).</td>
<td></td>
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<tr>
<td><strong>c.</strong> I have the right to question my doctor about the safety of taking (medication) during my pregnancy.</td>
<td></td>
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</table>

MEDICATION USAGE

Since you first called Motherisk, have you changed the way you take [prescription medication]? (Ask participant to quantify.) Was this change recommended by anyone? Who?

Now I have a few questions about the Motherisk service itself. I’d like to remind you that your answers will be kept entirely confidential.

SATISFACTION

<table>
<thead>
<tr>
<th>Number 1-5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a.</strong> The counsellor spent enough time explaining the risks of using this medication during pregnancy.</td>
<td></td>
</tr>
<tr>
<td><strong>b.</strong> The counsellor treated me with respect.</td>
<td></td>
</tr>
<tr>
<td><strong>c.</strong> The counsellor seemed to care about my concerns about using this medication during pregnancy.</td>
<td></td>
</tr>
<tr>
<td><strong>d.</strong> The Motherisk service is convenient to use.</td>
<td></td>
</tr>
<tr>
<td><strong>e.</strong> I was satisfied with the service I received from Motherisk.</td>
<td></td>
</tr>
</tbody>
</table>

"Overall, do you have any comments about your experience with calling Motherisk?"

Thank you.
APPENDIX 4 – Ethics Approvals
October 30, 1998

Ms. Colleen Duncan
Division of Clinical Pharmacology & Toxicology
The Hospital for Sick Children

Dear Ms. Duncan

Your study “Pilot Study: Effectiveness of risk-counselling (Motherisk) on prescription medication self-management practices”

REB File No. 98/094

On behalf of the Research Ethics Board, I approve the modification to the above noted study as described in October 22nd correspondence.

Yours truly

Aideen Moore, MD, MRCPI, FRCPC
Chair, Research Ethics Board
THE HOSPITAL FOR SICK CHILDREN

RESEARCH ETHICS BOARD

Approval & Terms of Agreement

APPLICANTS: Ms. C. Duncan & Dr. G. Koren

PROJECT TITLE: Pilot Study: Effectiveness of risk-counselling (Motherisk) on prescription medication self-management practices

FILE NUMBER: 98/094

MEMBERS OF THE BOARD*: Dr. A. Moore, Chair
Dr. B. Stevens
Dr. M. Rossi
Dr. A. Taddio
Dr. D. Bagli
Dr. B. McCandie
Dr. M. Crawford
Ms. S. Doyle

Dr. M. Dennis
Ms. J. Clarkson
Mrs. B. Benoliel
Ms. M. Rowell
Dr. C. Cirilli
Dr. S. Baruchel
Dr. A. Feigenbaum

*Meeting may not have been attended by all members.

I agree to carry out the proposed research involving human subjects in accordance with the protocol approved by the Research Ethics Board using the approved consent forms. I shall notify the department/division chief and the Research Ethics Board prior to implementing any modifications in the protocol and of any adverse or unexpected events as soon as possible.

SIGNATURE (INVESTIGATOR) Collen Duncan DATE Aug. 24/98

I agree to monitor the protocol on an ongoing basis, and to notify the Research Ethics Board as appropriate.

SIGNATURE (DEPARTMENT/DIVISIONHEAD) DATE Aug. 25/98

The Research Ethics Board of the Hospital for Sick Children has reviewed and approved the above-named project.

Chair, Research Ethics Board

DATE OF APPROVAL AUG 28 1998
EXPIRY DATE AUG -- 1999
APPENDIX 5 – Sample Motherisk Statements
MOTHERISK STATEMENTS

2-(2-METHOXYETHOXY)ETHANOL (See Methoxy ditycol)

5-AMINO SALICYLIC ACID
5-aminosalicylate is one component of sulfasalazine. It is now used as monotherapy in the treatment of inflammatory bowel disease, either orally or by enema, and seems to have minimal systemic absorption. 5-aminosalicylate has not been associated with an increased risk of birth defects (Schardein, 1985). It is considered the drug of choice for treatment of inflammatory bowel syndrome in pregnancy (Maternal Fetal Toxicology; Koren, 1990). J. 1980.

5-FLUOROURACIL
5-fluorouracil is a pyrimidine analogue. When given systemically it is known to be a potent teratogen in all animals studied. There is limited experience during pregnancy in humans. Four cases have been reported. Two exposures during the first trimester resulted in normal neonates, while a third had multiple congenital defects including radial aplasia, imperforate anus, and other organ involvement (Am J Obstet Gynecol, 1980). The fourth exposure occurred during the third trimester. The child was born cyanotic with jerking extremities.

The teratogenic risk of vaginal 5-fluorouracil is not entirely clear, however, two patients who became pregnant during topical vaginal 5-fluorouracil treatment had healthy newborns with normal developmental landmarks at 6 months of age (Am J Obstet Gynecol 1990;163:76-7). Vaginal absorption is probably about 10%, since systemic absorption of topical doses is 5-10% (Am Hosp Form). s.f. 1986.

3,4-DIAMINOPYRIDINE
The use of diaminopyridine in myasthenia gravis is experimental. No animal or human teratogenic data is available for 3,4-diaminopyridine. Diaminopyridine stimulates release of acetylcholine from the presynapse. A structurally related compound, 2,4-diaminopyridine, is not teratogenic in animals, even at high doses (100mg/kg/d). Decreased birth weight and neonatal survival occurred at the highest doses, 100mg/kg/d. No human data is available for this drug. d.f. 1990.

ACEBUTOLOL
Acebutolol is a β-adrenergic blocker. There are no reports of fetal malformations due to exposure to this drug, but few data are available. Newborn infants exposed to β-blockers in utero should be observed for signs of β-blockade (bradycardia, hypotension and hypoglycaemia) in the post-natal period (Briggs). s.f. 1991.

ACETAMINOPHEN
Acetaminophen is believed to be non-teratogenic in humans (Schardein, 1985). However, existing studies have not assessed the effect of very high dosage (Briggs, 1986). In a single case report, Char et al (J Pediatr, April 1975, p. 638) described a woman who consumed 1.3 grams of acetaminophen daily throughout pregnancy. The woman was very sick herself and needed several transfusions for severe anemia. During the fifth month polyhydramnios developed which required eight amniocentesis recovering 16 liters of fluid. The infant died from severe renal insufficiency which the authors tried to relate to acetaminophen nephropathy.

ACETAMINOPHEN OVERDOSE & N-ACETYLCYSTEINE therapy
Acetaminophen is the most common overdose in pregnancy. Hepatic toxicity is consequent to the formation of a highly reactive intermediate (N-acetyl-p-benzo-quinonimine, [NABQ]), produced by acetaminophen metabolism through the cytochrome P₄₅₀ mixed-function oxidase (MFO) system (Mot Pharmacol 1980;18:536-42). Normally, NABQ is detoxified by glutathione, but overdose may increase the levels of NABQ which deplete endogenous glutathione stores. Thus more intermediate is available to react with and destroy hepatocytes. In adult overdose situations, when glutathione depletion reaches 70% of normal (~16 grams for a 70kg adult), insufficient detoxification occurs and an antidote (N-acetyl-cysteine, NAC, Mucocyst®) is required. Plotting acetaminophen plasma concentrations (µg/mL) after a single acute ingestion on the Rumack-Matthew nomogram permits prediction of hepatotoxicity and consequent need to treat with NAC.
Antidote: the protocol for intravenous treatment with NAC consists of a loading dose of 150mg/kg given over 15 minutes, followed by 50mg/kg over the next 4 hours, followed by 100mg/kg over the next 16 hours; initiation of therapy more than 16 hours after acetaminophen overdose is not recommended (Br Med J 1979;2:1097-1100).


In the largest study to date of acetaminophen overdose in pregnancy (Obstet Gynecol 1989;74(2):247-53), time to NAC loading dose and gestational age at the time of maternal overdose are most predictive of fetal death (chances for fetal demise increase with a longer gap time between ingestion and NAC treatment). No correlation existed between pregnancy outcome and the total number of maternal NAC doses, the maternal acetaminophen level, or the maternal peak aspartate amino-transferase level.

Pregnancy outcome and laboratory data was available for 60 pregnant women. Of these, 19 over-dosed in the first 13 weeks (6 SA, 8 TA, 5 normal, live births with no congenital anomalies), 22 in weeks 14-26 (2SA, 1 TA, 19 normal, live births) and 19 in weeks 27-39 (1 stillborn, 18 live births). Of the 42 live births and 9 fetal deaths, there was only 1 congenital defect in an infant born to a mother who was treated during the third trimester. Based on this rate (1/51, 2%), it cannot be concluded that either acetaminophen overdose or NAC is teratogenic.

NAC undergoes placental transfer in rats (Pharmacometrics 1983;26:249-60), but is clinically insignificant in sheep (Ann Emerg Med 1991;20:1069-72) and in humans (Personal communication; Simone C, 1993). In an in vitro placenta perfusion model, bolus NAC administration to the maternal side (3 placentas tested) resulted in fetal-side NAC levels below the lower limit of detection for the assay (50ng/mL) at 30-120 minutes post administration. Similarly, under conditions which mimicked maternal steady-state concentrations (2 placentas tested), levels in the fetal-side were below detection.

Given that the fetus has a low intrinsic risk for hepatotoxicity from maternal acetaminophen overdose and that NAC does not cross the human placenta in significant quantities, the management of the pregnant woman with an acetaminophen overdose should be no different from that of the non-pregnant patient (Maternal-Fetal Toxicology, p 89-114). This should include stabilization, supportive care, appropriate gastrointestinal decontamination and NAC therapy, based on serum acetaminophen concentration ascertainment and plotting on the nomogram. In summary, it appears that the fetus is not at increased risk for major malformations following NAC therapy in acetaminophen overdose situations. Pregnant women who present with acute acetaminophen overdose and potentially toxic serum levels should be treated with NAC as soon as possible. a.p. 01.11.93

ACETAZOLAMIDE

Acetazolamide (Diamox®) is a carbonic anhydrase inhibitor.

It has shown variable reproductive effects in animal studies; it is associated with skeletal abnormalities in rodents and rabbits, but not primates (Reprotox, 1991).

The manufacturer, Storz Canada has 11 spontaneous reports of fetal exposure. Indications for maternal medication were stated in only 4 cases: seizure disorder, glaucoma, or pseudotumour cerebri (2 cases). Duration of therapy was not stated. Outcome information was available for 5 cases: various hearing, learning and neurologic problems in a child whose mother was also on "anticonvulsants", VSD, multiple malformations (arm, toe, mouth) and respiratory distress syndrome, and premature delivery with neonatal acidosis.

The Collaborative Perinatal Project studied 1024 women with exposure to this drug at some time during pregnancy, and found no increase in the risk of malformations (Heinonen, 1977). Retrospective surveys have not demonstrated a reproductive risk (Ann Med Psychol 1967;389) (Med J Aust 1965;2:689-693). There is 1 case report of a sacrococcgeal teratoma in a neonate exposed to acetazolamide from conception to 19 weeks; however, the mother was taking other drugs (JAMA 1978;240:251-2).

In summary, this drug does not represent a teratogenic risk. However, the case report of neonatal acidosis may be a potential neonatal complication of exposure. l.m. 20.04.93

ACETIC ACID

Acetic acid is a two-carbon acid found in vinegar. There are few data on possible teratogenicity of this compound (Reprotox, 1990). In humans, acetic acid is a respiratory irritant. It is unlikely that the usual exposure of pregnant women to this agent would result in significant accumulation of the chemical. s.f. 05.01.91

114
APPENDIX 6 – Before/After Scores For All Questions in Each Domain

Knowledge-a: Taking (medication) during pregnancy will not increase the chances of birth defects.

Knowledge-b: Right now I have enough information about (medication) to decide if it’s safe to use in pregnancy.
Knowledge –c: I understand the information I have about (medication) during pregnancy.

Knowledge –d: I trust the advice I have already received about taking (medication) during pregnancy.
Perceived Legitimacy -a: Before becoming pregnant, I was satisfied with (medication) as a treatment for (medical condition).

Perceived Legitimacy-b: Now that I am pregnant I am satisfied with (medication) as a treatment for (condition).
Perceived Legitimacy-c: To stay healthy during this pregnancy it's important for me to take (medication).

Perceived Legitimacy-d: To keep the baby healthy during pregnancy, I need to keep myself healthy by taking (medication).
Sense of Empowerment-a: During pregnancy I have the right to decide whether or not to take (medication).

Sense of Empowerment b: During pregnancy I have the right to decide how much (medication) I'm going to take even if it's different from what my doctor prescribed.
Sense of Empowerment c: I have the right to question my doctor about the safety of taking (medication) during my pregnancy.