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The Determinants That Are Associated With Women Deciding To Take Long-Term Preventive Hormone Replacement Evaluated In The Context Of The Decision Support Framework

An exploratory analysis of a clustered randomized clinical trial evaluating a decision support intervention

By

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A thesis submitted to the School of Graduate Studies and Research in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology

University of Ottawa

June 2000

0-612-57099-1

Abstract

Objectives: 1) Primary, to identify factors influencing the decision to take long-term preventive hormone replacement therapy (LTP-HRT) assessed 2 months after the counseling interview with the physician. 2) Secondary, to identify factors influencing the decision to take LTP-HRT assessed after reviewing a decision support intervention and after a counseling interview with their physician and to identify the factors that are associated with women being uncertain regarding the decision to take LTP-HRT.

Method: Data, collected from women who were participating in a RCT to evaluate the effectiveness of a decision support intervention, was used to develop multivariate statistical models at three specific time points. The time points were after reviewing the decision support intervention, after a counseling interview with their physician, and 2 months after the counseling interview. The physician was the unit of randomization in the original study and thus multivariate statistical modeling adjusting for correlated observations using Generalized Estimating Equations was utilized.

Results: Factors influencing the preference to take LTP-HRT after reviewing a decision intervention and before visiting the physician include having had a hysterectomy and placing a high value on the importance of heart disease and a low value on the importance of breast cancer. Factors influencing the decision to take LTP-HRT after the counseling interview include the preference of the physician, the presence of physical and vasomotor symptoms as measured by the MENQoL physical and vasomotor subscales. Factors influencing the decision of a woman to take LTP-HRT two months after the counseling interview include the preference of the physician, the presence of psychological symptoms as measured by the MENQoL psychological subscale, and having low uncertainty as measured by the DCS uncertainty subscale. Factors were also evaluated to identify women who were uncertain regarding the preference to take LTP-HRT after the decision intervention. Women were more likely to be uncertain if they placed a high value on the importance of osteoporosis, had a high level of uncertainty as measured by the DCS and had decreased satisfaction with the decision and the decision-making process as measured by the DCS.

Conclusion: At different time points in the decision process, the factors varied in what was associated with the decision. This may show that different factors are important depending on where the woman is in the decision-making process, conversely, it may be related to the small sample size of the dataset used for the analysis. The physician preference was a significant factor in predicting the decision both after the counseling interview and in the long-term decision to take LTP-HRT. The physician may be affirming the decision of the women to take LTP-HRT or the physician may be guiding the women to the decision. The interaction between the patient and the physician needs to be studied in more detail to determine the nature of the relationship between the patient and the physician and the extent of each of their contributions to the decision. The DCS, uncertainty and satisfaction subscales were important in identifying women who were uncertain in their preference towards LTP-HRT. These two subscales of the DCS could be used to identify women who may require the implementation of more health care resources in order to reach a decision that the women is comfortable with and able to implement regarding the use of LTP-HRT.

Acknowledgements

I would like to express my gratitude to the following people. I am grateful to George Wells for his supervision, guidance, and support through this project. George was always able to grasp the analytical complexities that we would run into and set me on the correct path for resolution. I am appreciative of his encouragement and support of my career development and I look forward to the opportunity to work with George on future projects. I am thankful to Annette O'Connor for her co-supervision, and knowledge of HRT and decision-making. Annette always understood the big picture and the importance of this project. I appreciated her words of encouragement and her enthusiasm for this project. I appreciated Ian Graham for his insights into physician behaviour and ideas for future research questions to consider. M.J. Jacobsen (research coordinator of the original study) and My-Linh Tran (database manager) were always available to answer questions and this project could not have been completed without their assistance. Last, but most important, my husband Joe Tauskela and our two children, Laura and Lisa. Both maternity leaves occurred during my enrollment in the masters programme and without their support and understanding I would never have completed this project.

The original study was supported by the Arthritis Society Research Grant no. 864.

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Glossary

ACP	American College of Physicians
CHD	Coronary Heart Disease
CI	Confidence Interval
DA	Decision Aid
DCS	Decision Conflict Scale
DSF	Decision Support Framework
FHx	Family History
HERS	Heart and Estrogen/progestin Replacement Study
HL	Hosmer and Lemeshow Goodness of Fit Statistic
HRT	Hormone replacement therapy
JAMA	Journal of the American Medical Association
LTP-HRT	Long-term preventive hormone replacement therapy
MENQoL	Menopause Quality of Life Scale
MeSH	Medical Subject Headings
MCS-12	Mental Component Summary subscale of the SF-12
NPHS	National Population Health Survey
OR	Odds Ratio
PCS-12	Physical Component Summary subscale of the SF-12
PDM	Participatory Decision-Making Style
RCT	Randomized Controlled Trial
SF-12	A multipurpose short form generic measure of health status
T0	Time 0
T1	Time 1
T2	Time 2
T3	Time 3
VTE	Venous Thromboembolic Events

1. Introduction and Objectives

1.1 Introduction

This study identifies the factors that influence the decision of post-menopausal women to take hormone replacement therapy for long-term prevention (LTP-HRT). Long-term prevention implies the use of hormone replacement therapy (HRT) for a period of greater than 5 years to prevent or delay osteoporosis and heart disease in post-menopausal women. The decision by a woman to take LTP-HRT is made with considerable uncertainty. Physicians and health care practitioners remain polarized on who should receive LTP-HRT. As recommended by the following medical societies, the American College of Physicians, the Society of Obstetricians and Gynaecologists of Canada, and the Osteoporosis Society of Canada, women should participate in this decision-making process to take LTP-HRT[1-3]. Women should participate in the decision making process because the current scientific uncertainty regarding benefits and risks of the treatment makes the decision very difficult. The decision requires consideration of a woman's personal values and willingness to tolerate the various risks associated with the possible outcomes. When considering LTP-HRT, women need to be informed about the options that are available to them, and the potential outcomes and benefits associated with their decision.

For medical decisions that do not have an accepted practice of standard, O'Connor[4] has developed a framework, the Decision Support Framework (DSF). The goal of the DSF is to enable the patient and the practitioner to make a high quality decision. The DSF is employed in those situations where decisions require reflection, consideration and application of personal values. The DSF is based on social support theories. The DSF provides a framework that enables the patient and the practitioner to address a decision, taking into consideration the patient's sociodemographic and clinical characteristics. As part of the DSF, a decision support intervention is utilized to improve knowledge, ensures that expectations are realistic, and explicitly clarify the importance that is placed by the patient on the risks and benefits. Persistence and satisfaction with the decision and the decision-making process are consistent with a high quality decision.

Several previous studies have examined factors associated with the use of LTP-HRT but none have considered the process of decision-making made by the patient and the physician. In view of the scientific uncertainty regarding the risks and benefits of LTP-HRT, factors, which influence the decision, assume great importance. The DSF provides a framework that allows the woman and the physician to identify these factors. For the woman and her physician identification of factors that are important to the woman will lead to a more appropriate decision regarding LTP-HRT. Specific areas could be identified by the woman and the physician that needs to be targeted for increased clarification and support of the patient in the decision-making process. The results of the current study will allow evaluation of the factors influencing the decision in the context of the DSF will allow one to better understand the decision-making process. This information will help to improve the process of informing women and their physicians about their impact on the decision-making process and help the physician to provide better support in the decision process.

1.2. Objectives

1.2.1. Primary Objective (Decision Two Months after the Counseling Interview)

The primary objective of this study was to determine the factors influencing the decision to accept and initiate LTP-HRT by post-menopausal women. This was the decision assessed two months after the counseling interview. Each woman had utilized a decision support intervention and had a counseling visit with her family physician.

1.2.2. Secondary Objectives

1.2.2.1. Secondary Objective 1 (Preference after the Decision Intervention)

The secondary objective 1 of this study was to determine the factors influencing the decision to consider LTP-HRT by post-menopausal women. This was defined as the preference of the woman within 24 hours of reviewing the decision support intervention.

1.2.2.2. Secondary Objective 2 (Decision after the Counseling Interview)

The secondary objective 2 of this study was to determine the factors influencing the decision to accept LTP-HRT by post-menopausal women. This was defined as the initial decision of the woman within 24 hours of the counseling visit with her physician.

1.2.2.3. Secondary Objective 3 (Change of Opinion after the Counseling Interview)

The secondary objective 3 of this study was to determine the factors that influencing those women who changed their opinion regarding the use of LTP-HRT. The change in opinion is measured between the following two time points, following review of the decision support intervention, and following the counseling visit.

2. Background

2.1. Hormone Replacement Therapy

2.1.1. Practice Guidelines and Recommendations for the use of LTP-HRT

Practice guidelines and the recommendations for the use of LTP-HRT are not yet set. They change with each new reported study that examines the benefits and risks. Numerous medical societies having an interest in osteoporosis, cardiovascular disease, and the general health of postmenopausal women have reviewed the current evidence regarding the risks and benefits of LTP-HRT[1-3]. The recommendations by these societies agree in one aspect. With the current state of knowledge, postmenopausal women are uncertain regarding whether or not the risks of LTP-HRT outweigh the benefits. Given the scientific uncertainty, it is therefore recommended that the tolerance of each woman to the risks and benefits of LTP-HRT be taken in to account in the decision-making process.

Grady et al. published the guidelines for counseling postmenopausal women about preventive hormone therapy for the American College of Physicians (ACP)[1]. The ACP recommended that all women should consider preventive hormone therapy stating that 'Women who have had a hysterectomy were likely to benefit from estrogen therapy. Women who have coronary heart disease (CHD) or who are at increased risk for CHD are likely to benefit from hormone therapy. The risks of hormone therapy may outweigh the benefits in women who are at increased risk for breast cancer; and for other women, the best course of action is not clear'[1].

The Scientific Advisory Board of the Osteoporosis Society of Canada does not recommend HRT for all postmenopausal women. This board also believes that women should understand the benefits and risks of LTP-HRT, consider their personal values and participate with their physician in decision-making. They believe that women at risk of osteoporosis should consider taking LTP-HRT[3].

The Society of Obstetricians and Gynecologists (SOGC) Menopause Consensus Committee believes that the benefits of HRT greatly outweigh the risks, stating that 'Every Canadian woman should have individualized care and be offered the benefits of HRT'. She, with an informed physician, can then decide on her course of action[2].

The recommendations from the societies described above were all published prior to the publication of the Heart and Estrogen/progesterone Study (HERS)[5]. These societies are currently revising their recommendations regarding HRT use in the postmenopausal women with established heart disease. The American College of Cardiology and the American Heart Association have revised the recommendations for HRT use in patients experiencing an acute myocardial infarction. They do not recommend starting HRT after a myocardial infarction but women who are already on therapy can continue[6].

Summarizing the guidelines from these societies, women should be involved in weighing the benefits and risks of LTP-HRT and make an informed decision about the use of HRT based on the best available evidence. Implementing these guidelines is challenging, mainly because of their contradictory nature of the benefits and the risks.

Judging the benefits and risks of LTP-HRT is complex. Moreover, imparting this information in an easily understood fashion to post-menopausal women is difficult. Given the limited resources to support decision-making in our current health care system, health care professionals need a better understanding of factors influencing the decision to take LTP-HRT in post-menopausal women. This would aid in assisting women in making an appropriate decision[4].

2.1.2. Benefits of LTP-HRT

It is well accepted that the presence of climacteric symptoms during the peri-menopause period is a reason to treat with hormone replacement therapy[1-3]. Climacteric symptoms usually include hot flushes, vaginal dryness, urinary frequency, insomnia, and depression or irritability[1]. Hot flushes and the other vasomotor symptoms usually stop within three to five years and therefore require HRT for short-term relief. Genitourinary symptoms are often not relieved by systemic HRT and require local vaginal estrogen therapy[1].

The currently accepted benefits of long-term prescription of HRT are for prevention of osteoporosis and heart disease[1; 3]. Other less well established benefits of LTP-HRT include: the preservation of skin elasticity; improved symptoms of urinary incontinence, frequency, and urgency; improved sexual function; improved verbal memory in older women; and improvements in women with mild or moderate symptoms of Alzheimer disease[7; 8].

2.1.2.1. Review of the Evidence for the Prevention of Cardiovascular Disease

Numerous observational studies estimate that estrogen users have a 35-50% reduction of risk of cardiovascular disease [7-11]. Furthermore, observational studies of women with known pre-existing cardiovascular disease at the time of initiation of HRT have demonstrated a reduction of 35 - 80% in subsequent morbidity and mortality as compared to non-users[5]. The majority of the observational studies conducted used unopposed estrogen[12]. The addition of progesterone eliminates the risk of uterine cancer in women who have not had a hysterectomy.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [12] and the Nurses' Health Study [13] studied estrogen and progesterone in combination. The PEPI trial was a randomized double-blind placebo controlled trial that studied healthy postmenopausal women aged 45 to 64 years randomized to various combinations estrogen and progesterone. The primary outcomes were surrogate endpoints of cardiovascular disease. The study showed that the addition of progesterone to the regimen did not have a statistically significant effect on the lipoprotein profile as compared to estrogen alone. The Nurses' Health Study was a prospective cohort study that found no differences in risk of coronary heart disease in postmenopausal women between estrogen and estrogen/progesterone users. These two studies indicate that the addition of progesterone to estrogen does not diminish the beneficial effects of the estrogen on the lipoprotein profile. The impact on the risk of CHD may still not be adequately studied as neither study evaluated clinically relevant cardiac events as the outcome of interest[8].

The 1998 HERS study was the first published randomized, double blind, placebo controlled trial to evaluate the effect of HRT use in postmenopausal women with already established CHD[5]. This study evaluated an older population (average age 66.7 years) of 2763 postmenopausal women with various forms of established heart disease, which included: previous myocardial infarction, coronary artery bypass grafting, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries. The primary outcome of the study was nonfatal myocardial infarction or death due to CHD. The study had an average duration of follow-up of 4.1 years. No statistically significant difference was found between the two groups with respect to the primary outcome or any secondary cardiovascular outcomes. There was a trend to more primary outcomes in the first year in the hormone users but a decreased risk of primary outcomes in subsequent years.

The HERS study was also the first randomized controlled trial (RCT) study published on HRT use in postmenopausal women using a clinically relevant outcome[5]. The results of this study were dramatically different from the results of previously published observational studies that assessed the relative risk reduction of heart disease in women who used HRT. An editorial by Petitti in the same issue of the Journal of the American Medical Association (JAMA) states that the nature of the design of the study may be the reason for the difference in results[14]. Observational studies are more likely to have selection bias, involving women with healthy behaviours who may selectively use HRT. The HERS study was a RCT and thus avoided this bias. A more detailed analysis of the data from the HERS article revealed that within the overall null effect, risk for CHD was reduced in years 3 to 5, but this reduction was offset by a surprising 50% increase in risk during the first year [15]. The HERS study was a secondary prevention trial for women with established CHD considering LTP-HRT. No data is available for follow-up periods longer than 5 years so long-term effects for secondary prevention are still unclear.

The results of the HERS study cannot be extrapolated to women considering LTP-HRT for primary prevention of CHD. The Women's Health Initiative, an RCT that will report on results in 2005, addresses primary prevention of coronary heart disease in postmenopausal women[5; 14]. The participants in the Women's Health Initiative are not required to have CHD and are generally younger than the HERS population[5; 14]. At the time of the reporting of this trial, they will have approximately 10 years of follow-up. Thus, the ACP current recommendations still hold for women who have no history of heart disease.

2.1.2.2. Review of the Evidence for the Prevention of Osteoporosis

Epidemiological studies have shown that current users of HRT have a 50% reduced risk of vertebral fractures and a 25% reduced risk of hip fracture [9; 10]. Fifty percent of bone loss occurs within the first five to seven years following menopause. Provided that HRT is administered within five to seven years following menopause, bone mineral density (BMD) reverts to pre-menopausal levels[16]. Withdrawal of estrogen results in a recurrence of menopausal remodeling dynamics and bone loss. The longest follow-up study of women placed on LTP-HRT in the early menopause is 10 years[16] and a decline in bone mass appears to occur at the end of this period.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was a randomized double-blind placebo controlled trial that studied healthy postmenopausal women aged 45 to 64 years randomized to various combinations estrogen and progesterone. One of the outcomes were surrogate endpoints of osteoporotic disease. The study showed that treatment with combination therapy over three years increased bone mineral density as compared to placebo[17], thus supporting previously published observational and small short-term randomized controlled trials. The HERS study as a secondary outcome evaluated osteoporotic fractures in the treatement and placebo group[5]. With an average follow-up of 4.1 years there was no difference in the number of fractures between the two groups with the placebo group having 138 fractures and the treatment group having 130 fractures ($p=0.59$). The women in the HERS study were of older age (average age of 66.7 years) and it is unclear if estrogen has an effect on bone remodelling beyond the early menopausal years.

The Women's Health, an RCT that will report on results in 2005, addresses primary prevention of osteoporosis in postmenopausal women[5; 14]. At the time of the reporting of this trial, they will have approximately 10 years of follow-up. This will be the first study that can answer the following questions rgarding the use of LTP-HRT: first, whether BMD is an appropriate surrogate marker for osteoporotic fracture and second, if the effects of estrogen and progesterone are maintained long-term. Osteoporotic fractures are primarily a disorder of older women. Taking into account the average life span and onset of menopause, LTP-HRT would have to be taken for at least 25 years to prevent fractures and the usefulness of 5-10 years of LTP-HRT on the long-term result of osteoporotic fracture is still unclear. LTP-HRT leads to a reduction in the rate of bone loss in the post-menopausal years but it is unclear if this benefit continues to exist beyond 10 years of treatment.

2.1.3. Risks of LTP-HRT

2.1.3.1. Review for the Causation of Breast Cancer

The results of LTP-HRT on the risk of breast cancer in epidemiological studies are controversial. The most consistent finding has been an increased risk of breast cancer after HRT use greater than 15 years[8; 11]. A decision-analysis published in 1994 by Gorsky et al.[11] predicted that LTP-HRT use greater than 15 years would lead to an increase of deaths in breast cancer by 21% as compared to non-users but that the risk of breast cancer does not change for use of HRT of less than 5 years [11]. In a comprehensive review of the literature, Grady et al[7]. quote a relative risk of 1.25 for developing and dying of breast cancer in hormone users as compared to non-users, when HRT use has been longer than 5 years. With short-term use of HRT, less than 5 years, there is no increased risk of breast cancer[7]. HRT may also affect the results of mammography, leading to more false positive rates and thus raising anxiety among women[8].

2.1.3.2. Review of other Risk Factors

Estrogen can cause dose-dependent unpleasant side effects such as bloating, breast tenderness, and headache[7]. These side effects occur in approximately 5 - 10% of women taking standard-dose estrogen [7]. Long-term use of unopposed estrogen increases the risk of endometrial cancer, but this risk is reduced to the level of the non-user of HRT by the addition of progesterone[7]. Recent observational studies have suggested that the relative risk of venous thromboembolic events in estrogen and estrogen-progesterone users was three times higher than non-users[5]. The HERS study shows that the excess incidence of venous thromboembolic events (VTE) was 4.1 per 1000 women-years of observation, an order of magnitude higher than the excess reported in observational studies. The authors of the HERS study postulate that the reason for the differences is the older population had more risk factors and only idiopathic events were counted in the observational studies[5].

2.1.4. Current Use of LTP-HRT

Even with inconsistent scientific evidence, a large number of Canadian women have decided to use HRT. The first national report of HRT use among Canadian women draws upon data from the National Population Health Survey (NPHS)[8]. According to the 1994/95 NPHS, 22% of women aged 45-64 used some form of HRT for menopause symptoms in the month before they were interviewed. Use was highest among those aged 50-54 (33%), which corresponds to the age of women when symptoms of menopause are likely to be most numerous. From the NPHS data it is not possible to assess whether lower HRT use among older women results from their refusing the therapy, discontinuing it or not being offered it by their physicians.

A United States survey of older women (aged 65 years or older) who participated in the Multicentre Study of Osteoporotic Fractures found that 17.4% of the population were currently using oral estrogens, 27.2% were past users, and 55.4% had never used oral estrogen therapy[18]. The primary reasons for initiating HRT use were menopausal symptoms, having received a prescription from their physician, or osteoporosis prevention or treatment. For past users the reasons for starting HRT use were similar to current users. The main reasons for stopping estrogen therapy included feeling they no longer required HRT and undesirable side effects. The main reasons that these women gave for not using HRT were the medication might be harmful or not required[18].

In summary, the decision to take LTP-HRT is subject to uncertainty. Studies of the risks and benefits are limited and offer contradictory recommendations, especially when long-term use is being considered[8]. Critics of LTP-HRT feel that the benefits are often overstated and the risks understated. The majority of the literature is based on epidemiological or observational studies. Therefore, many of the observed favourable effects may be biased in favour of the sociodemographic characteristics of women who use HRT and of those who agree to participate in HRT studies[8].
It is currently recommended that the decision needs to be made after a careful review of the known benefits and risks of the treatment. Furthermore, there needs to be a careful assessment of the importance that a woman places on the risks and benefits. Ultimately the woman will make the decision herself or in combination with her physician with imperfect information[4; 9].

2.2. Frameworks for Understanding Decision-Making in the Clinical Encounter

Making a decision can be a very complex process and medical decision making is particularly challenging due to the urgency, complexity, and uncertainty that is characteristic of many clinical situations[19; 20]. Eddy has outlined two steps that are required to make a decision regarding medical care[21]: first, the outcomes of the alternative practices must be estimated; and second, the desirability of the outcomes of each option must be compared. The first step is often a question of facts. It is reasonable to assume that one correct answer exists, however, estimation of the outcomes are subjective as the data available is usually never complete. The second step is a question of personal preferences of the patient which may be influenced by the preferences of the physician.

The model that best describes the role of the physician in the traditional patient-physician relationship has been one of paternalism[22]. This model makes a number of assumptions[23]: first, the patient and the physician have the same goals; second, physicians can judge patient preferences; third, only the physician has the experience to determine what should be done; and last, the patient should be spared the worry of decision making or even deceived in order to engender faith, reassurance, and hope.

More recently, other models of the patient-physician interaction have been described focusing on the nature of the decision-making process[23-28]. Shared decision-making is increasingly advocated as the ideal model of decision-making for patient and physician interactions[26]. The effects of patient consumerism on the physician-patient relationship and the development of clinical guidelines are generating intense interest in how patients make decisions[29]. Charles et al. outlines four characteristics that are necessary to fulfill the model of shared decision-making[26]: first, shared decision-making involves at least two participants, for example the physician and the patient; second, both parties (physicians and patients) take steps to participate in the process of treatment decision making; third, information sharing is a prerequisite to shared decision making; and fourth, a treatment decision is made and both parties agree to the decision. Patients bring to the relationship their "personal moral values or life-style preferences" and physicians bring their expertise about the technical aspects of diagnosis and management[23]. An emphasis on shared decision making requires abandonment of the assumption that for most medical decisions there is an answer to the question, "Who should decide?"[23].

Shared decision-making is a relatively recent concept in medicine. The majority of studies examining the decision-making process have focused on the informational needs of patients. These studies show that patients generally want detailed information about treatment options, risks, and benefits[25; 30; 31]. Deber[22], after reviewing the literature, concluded that almost all patients want information, but not all want to participate in decision-making. Recent research has demonstrated that most patients have a high desire for information but the desire for involvement in decision making varies substantially among patients[25; 32-36]. If patients are to be involved in the decision, they need an environment in which they feel independent and able to make decisions, their goals and values are understood and they are educated about the risks and benefits of treatment options[23]. In busy practices physicians rarely have enough time to gather and provide such information[23]. How patients make decisions will impact on the current debate about the allocation of scarce health-care dollars and what commitment would be required from health-care providers[29]

Some studies have found that patients have measurably better outcomes when preferences about treatment options are stated or taken into account[10; 37-40]. The positive effects of patient participation in decision-making may be for one of two reasons. First, the advantage of one treatment over another may be due largely, or entirely, to individual patient utilities for attributes of the treatments. Decisions made by patients may fit their preferences better than decisions made by physicians. Second, improved psychological outcomes resulting from patient participation in decision-making may be due to the empowerment gained when patients choose for themselves[39; 41]. Furthermore, patients who have participated in the decision making process are more likely to adhere to the decision [37]. Several studies have found that people who could attribute the choice of treatment to themselves responded more favourably to treatment than those who could not [39]. Laine et al[42]. postulate that the shared-decision making model has become the model most commonly used in clinical practice for two reasons: first, increased consumerism of patients; and second, to protect against uncertainty in medicine. Thus over time there has been a relaxation of social and political control over patient's lives by their physicians, leading to an increased willingness of physicians to involve patients.

Optimally, effective patient-physician communication should lead to better health outcomes for the patient. The communication between physicians and patients can be a source of motivation, incentive, reassurance, and support, as well as an opportunity for revision of expectations of both patient and physician[43]. The physician is in an unique position to influence the technical care of the patient and to persuade the patient to follow the dictates of that care, but also to change their perceptions of their health status and to provide motivation and incentives for engaging in health promotion[43].

Given the uncertainty of patient's desire for shared decision-making, many studies have attempted to evaluate which characteristics would predict the patient's desire for shared decision-making. Patient characteristics that have been shown to predict who would prefer to participate in shared decision-making include younger age, higher level of education, and female gender[25; 31; 34; 37; 38]. The desire of patients to participate in medical decision-making may also vary depending on the clinical situation. Degner et al[34]. demonstrated that patients with newly diagnosed cancer were less likely to be involved in the decision making process as compared to members of the general public.

The Medical Outcomes Study[38] is the largest study to date examining patient and physician characteristics that are predictive of shared decision making. This study explored the effects of patient characteristics, specifically age, education level, minority status, gender, and health status, as well as the duration of the physician-patient relationship and length of the office visit, on the participatory decision-making style (PDM) of the physician[38]. Of the patient characteristics age, was related to PDM in a complicated manner, with patients younger than 30 and older than 75 least likely to have participatory visits. An interaction existed between the age of the patient and the duration of the relationship with the physician: a longer relationship with the physician means more PDM only for those patients less than 65 years of age. Education, race and gender were significantly related to PDM. Patients with a high school education or less, minority patients, and males all had less PDM. The interaction of physician and the gender of the patient were statistically significant for male patients. A male patient-physician relationship was less likely to participate in PDM, but a male patient-female physician was more likely to participate in PDM. Better perceived health status by the patient and longer visits and longer patient-physician relationships were also related to more PDM[38].

Involving patients in treatment decisions requires a certain amount of time[38]. The patient's perspective can be decisive in choosing when to seek help, the degree of compliance with treatment, and whether to change one's lifestyle[20]. A patient who takes responsibility for a decision may also be less likely to blame the physician when a poor outcome occurs[20].

2.2.1. The Ottawa Decision Support Framework

O'Connor et al[4]. has developed a model the Decision Support Framework (DSF) that describes how to support and involve patients in decision-making. The DSF is based on expectancy value, decisional conflict, and social support theories. The model was developed for health decisions that meet the following conditions: first, a new circumstance, diagnosis, or developmental transition stimulated the need for a decision; second, the decision requires careful deliberation because of the uncertain and/or value-sensitive nature of the benefits and risks; and third, the decision needs relatively more effort during the deliberation phase than the implementation phase [4]. The DSF can be broken down into three components, as illustrated in Figure 1: first, assessing the determinants of the decision; second, providing decision support; and third, evaluating the decision-making and outcomes[4]. The following three sections will address the three components in more detail.

Figure 1. Decision Support Framework (DSF)

Assess Client & Physician Determinants of Decision	**Provide Decision Support Intervention (DSI)**	**Evaluate Quality of Decision and Decision Making Process**	**Evaluate Client Outcomes of Decision**
Sociodemographic & Clinical Characteristics	Tailor DSI to participant's characteristics	Satisfaction with decision support	Improved health related quality of life
Perception of the Decision: Knowledge, Expectations, Values, Decisional conflict	Clarify/Modify knowledge, expectations, values. Tailor DSI to factors contributing to decisional conflict	Improved knowledge Realistic expectations Improved clarity of values & value congruence with decision Reduced decisional conflict Reduced decision delay Satisfaction with decision	Reduced distress from consequences Reduced regret Appropriate persistence with decision
Perception of Important Others: Norms, Pressure, Support, Decision participation roles	Clarify/modify perceived norms Clarify pressure; Facilitate self-help skills handling pressure Facilitate access to support Tailor support to decision participation preferences	Realistic perception of norms and pressure Satisfaction with decision support	Appropriate persistence with decision
Resources to Make & Implement Decision: Personal resources, Experience, Self-efficacy, Skills, Motivation, Other resources, External resources	Enhance self-help skills preparing for, making, and implementing decisions and coping with consequences. Facilitate access to resources	Improved self-efficacy Improved decision making skills Decision implementation Improved knowledge of appropriate resources	Reduced distress from consequences Appropriate persistence with decision Appropriate and efficient use of resources Satisfaction with care

2.2.1.1. Determinants of the Decision

Determinants of decisions are the essential inputs that are required to make a decision. Determinants are unique to each patient and physician dyad, as each person brings their own unique sociodemographic and clinical characteristics to the decision. The choice of one alternative over another depends on more than the unique characteristics of the patient and the physician. The decision will also depend on their perception of the decision, the perception of others important to the patient, and the internal and external resources that each person brings to the decision-making process. The perception of the decision includes the knowledge of the patient and the physician about the issues and their expectation that the alternative chosen will lead to the outcomes that are valued higher by the patient. The perception of others important to the patient can include influence from sources not familiar with the woman involved in the decision, such as, the lay press, and media as well as family, friends, and health care professionals.

2.2.1.2. Decision Support

The second component of the framework is providing decision support. The goal of decision support is to improve decision making by addressing the modifiable determinants of the decision that are suboptimal. Decision support attempts to overcome inadequate knowledge, unrealistic expectations, unclear values, and unclear norms[4]. Decision support interventions are usually based on a decision analytic framework but do not formally combine utilities and probabilities [44]. The decision support intervention is a two step process: first, the physician and the patient are prepared for the decision-making process; and second, the structured follow-up process for the decision interaction is implemented.

2.2.1.3. Evaluation of Decision-making

The third component of the DSF is the evaluation of the decision-making process and the outcomes. The framework defines a high quality decision as one that is informed and congruent with the patient's values. The patient should also have low decisional conflict, little decisional delay, decision implementation, adherence to the decision, as well as satisfaction with the decision and the decisional process[4].

The goal of improving the quality of decision-making is to improve health outcomes of the patient which consist of an improvement in health-related quality of life, decreased distress from consequences, decreased decisional regret, appropriate and efficient use of resources, and long-term satisfaction with care.

2.3. Review of Previous Research on Determinants of Taking LTP-HRT

A systematic review was undertaken to better understand the decision of women to take LTP-HRT. The outcome was the actual decision to take HRT. The factors influencing that decision were defined in the context of the decision support framework. The three components of the decision support framework are the determinants of the decision, the decision support intervention, and the evaluation of the outcome of the decision.

2.3.1 Search Strategy and Selection of Studies

A computerized search of Medline (1966 - Jan1999), Healthstar (1976 – Jan1999), and Cumulative Index of Nursing and Allied Health (CINAHL) (1982 – Jan1999) was conducted. The search was limited to articles published in English. Decision-making is not an area that is well-indexed in electronic databases. A base search strategy was developed to identify all articles related to HRT and their relation to women who were post- menopausal. This strategy was limited to epidemiological studies. Review articles were excluded since only primary data sources were to be considered for analysis. The base strategy was then combined with text words and medical subject headings (MeSh) word searches for all the determinants from the DSF. The search strategy is outlined in Appendix 1. The reference list of each retrieved article was also searched for relevant articles. Also, content experts were interviewed to provide any studies from their personal files.

Articles were included if they had studied the decision to take HRT by post-menopausal women and reported on original data. In the study design at least two groups must be compared. The outcome was the actual decision to take HRT. Studies that reported on case scenarios or required the women to make a hypothetical decision were excluded.

2.3.2. Analysis

All studies that were included for analysis were classified according to a number of criteria including study design, definition of usage of HRT, and the type of analysis performed. For study design, the three major study designs were focus groups, cross-sectional surveys, or prospective cohorts. Since the primary outcome was the decision to take HRT, a prospective cohort design is a much stronger study design than a cross-sectional study. A prospective cohort follows the defined patient population and the decision is made during the study period. In a cross-sectional design, the decision to take HRT had been made prior to the study period. Both designs would be stronger than a focus group design.

For the definition of usage of HRT, many studies, particularly cross-sectional, defined the outcome or the decision to take HRT as the current use of HRT. Current use would be compared to never-users only or never-users and previous users combined. The outcome could also be defined as the ever-use of HRT (current users and previous users combined) and ever-use would be compared to never-use. The predictors of the outcome, the decision to take LTP-HRT, will be different for these various combinations.

For the type of analysis used in the study being reviewed, the three main types of analyses that were performed were qualitative, univariate, or multivariate. No further analyses were performed on studies that only had a qualitative or univariate analyses. For studies that used a multivariate analysis, the model building process was reviewed focusing on how variables were selected and whether interactions and confounding were considered.

2.3.3. Description of Studies

A total of 1,294 abstracts were obtained from the three databases. From this, 120 relevant abstracts were identified and the articles retrieved.

Forty-eight articles were found that met the inclusion criteria. The studies with a prospective cohort design are listed in Table 2.3.3.1. The studies with either a cross-sectional or focus group design are summarized in Table 2.3.3.2.

Table 2.3.3.1. Description of Prospective Studies Included in Review

Reference	n	Age	Hormone Use			Analysis	Determinants				Comments
			1	2	3		1	2	3	4	
Marks 1998[50]	3612	53-54	✓			LR	✓				Interaction
Collins 1997[103]	1190	52	✓			U	✓				
Moorhead 1997[77]	7612	PM		✓		U	✓				Nested case-control
Brett 1997[51]	2784	PM	✓			LR	✓				
Matthews 1996[104]	327	PM		✓		U	✓				Hysterectomy excluded
Jensen 1996[52]	413	45-58		✓		LR	✓				
Derby 1995[76]	842	PM		✓		U	✓				
Abraham 1995[80]	60	PM	✓			U	✓		✓		
Groenveld 1994[53]	1689	45-60			✓	LR	✓	✓			Interaction
Johannes 1994[49]	2224	45-55	✓			LR	✓		✓		Interaction
Egeland 1991[99]	179	PM	✓			U	✓				Hysterectomy excluded
Barrett-O'Connor 1989[100]	1057	50-79			✓	U	✓				
Phillipov 1997[45]	82	PM		✓		LR	✓				Post BMD
Langenberg 1997[46]	138	PM			✓	U	✓				Post hysterectomy
Larcos 1996[48]	80			✓		LR	✓				BMD clinic
Wallace 1990[47]	100	50-70	-	-	-	Q	✓				Distal radial fracture

Legend:
PM = post-menopausal
Hormone Use
Current and previous users versus never use. 2. Current users versus never users. 3. Current users versus previous and never users.
Analysis
LR = Logistic Regression, U = Univariate, Q = Qualitative
Determinants of Decision
1. Sociodemographic and Clinical Characteristics. 2. Perception of the Decision 3. Perception of Important Others. 4. Evaluation of Decision
Comments
Interaction implies that prespecified interactions were evaluated.

Table 2.3.3.2. Cross-sectional and Focus Group Studies in Review

Reference	n	Age	Hormone Use			Analysis	Determinants				Comments
			1	2	3		1	2	3	4	
Andrist 1998[105]	21	40-55	-	-	-	Q		✓	✓		Hysterectomy excluded
Newton 1998[54]	856	50-80		✓		LR	✓		✓		
Hunter 1997[106]	45	49-51	-	-	-	Q		✓	✓		
Leveille 1997[55]	521	>60			✓	LR	✓	✓	✓	✓	
Newton 1997[98]	1082	50-80	✓			U	✓				
Oddens 1997[56]	911	45-65	✓			LR	✓	✓			Interaction
McNagny 1997[57]	328	>40			✓	LR	✓		✓		African-american
Reference	**n**	**Age**	**Hormone Use**			**Analysis**	**Determinants**				**Comments**
France 1997[61]	211	PM	✓			LR	✓		✓		
Bastian 1997[62]	1566	45-51		✓		LR	✓				Previous use

											unknown
Stafford 1997[63]	6341	> 40			✓	LR	✓		✓		Interaction
Ghali 1997[64]	182	50-70			✓	LR	✓	✓	✓		
Walsh 1997[72]	126	45-55	✓			LR	✓	✓			
Handa 1996[58]	2602	>65		✓		LR	✓		✓		Interaction
Blumberg 1996[73]	212	>50	✓			U	✓	✓	✓		
Shelly 1995[65]	1642	45-55			✓	LR	✓	✓			Interaction
Salomaa 1995[75]	1202				✓	U	✓				
Griffiths 1995[107]		45-64			✓	U	✓				
Lancaster 1995[74]	1852	45-64		✓		U	✓				Interaction
Sinclair 1993[108]	492	33-69	✓			U	✓				
Hemminki 1993[59]	2000	45-64		✓		LR	✓				Interaction
Derby 1993[66]	3279	40-60			✓	LR	✓				5 sampling periods
Parazzini 1993[67]	1842	45-74	✓			LR	✓				
MacLennan 1993[68]	1047	>40	✓		✓	LR	✓				Hysterectomy excluded
Ringa 1992[69]	1986	45-55			✓	LR	✓				
Oddens 1992[70]	1223	>40			✓	LR	✓				
Logothetis 1991[109]	262	40-60	-	-	-	Q		✓			
Kadri 1991[79]	539	44-64	✓			U	✓	✓	✓		
Cauley 1990[60]	9704	>65		✓		LR	✓				Interaction
Barlow 1989[110]	424	40-60				Q	✓				
Ferguson 1989[78]	274	PM		✓		U	✓		✓		
Egeland 1988[71]	2137	40-52			✓	LR	✓				Interaction
Marmoreo 1998[111]	56	44-73	-	-	-	Q	✓	✓			Hysterectomy excluded

Legend: same as Table 2.3.3.1.

There were 16 prospective cohort studies of which four[45-48] investigated a specific sub-population of postmenopausal women considering HRT (Table 2.3.3.1.). Of these 4 studies, 2 studies examined women undergoing a bone mineral density test[45; 48], 1 evaluated a cohort of women post hysterectomy[46], and the final study examined women who had had a distal radial fracture[47]. Two of the four studies that analyzed a specific sub-population of women were analyzed using a multivariate analysis[45; 48]. These two studies only considered covariates of the decision from category one from the decision support framework. The sample size of these two studies ranged from 80 to 82.

Of the 12 remaining prospective cohort studies, 5 were analyzed using multivariate statistical techniques[49-53], of which 3 analyzed only covariates or predictors of the decision that were from the first category of the DSF (sociodemographic and clinical characteristics)[50-52]. One of these 5 studies analyzed covariates from the first category as well as the second category of the DSF (perception of the decision)[53]. The fifth prospective study with multivariate analysis analyzed covariate from the first category as well as the third category of the DSF (perception of important others)[49]. No prospective multivariate studies evaluated the evaluation of the decision as one of the predictors of the decision to take HRT. The 5 prospective multivariate studies ranged in size from 413 to 3612 patients. Three of the five studies that employed a multivariate analysis assessed for interactions[49; 50; 53].

There were 31 cross-sectional studies (Table 2.3.3.2.). Nineteen of the 31 cross-sectional studies were analyzed using multivariate techniques[54-72]. Five of the 19 studies compared the ever use of HRT to never use[56; 61; 67; 68; 72], 5 studies compared current users to never users (eliminating previous users from the analysis)[54; 58-60; 62], and 10 studies compared the current use of HRT to ever users[55; 57; 63-66; 68-71]. One study is counted twice as the analysis was repeated depending on the categorization of the previous users[68]. The 19 cross-sectional multivariate studies all evaluated covariates from the first category of the DSF (sociodemographic and clinical characteristics). Five studies also examined category two covariates of the DSF (perceptions of the decision)[56; 64; 65; 72; 73], seven studies considered category two covariates of the DSF (the perception of important others)[54; 57; 58; 61; 63; 64; 73], and only two studies considered covariates from all three categories of the DSF[64; 73]. One study considered the evaluation of the decision as a predictor of the decision[55]. Nine of the 19 studies that employed multivariate techniques of analysis tested for interactions or presented a stratified analysis on covariates that they felt a priori were important[54; 56; 58-60; 63; 65; 71; 74].

2.3.4. Results

The variables that are included in the decision support framework and the studies that indicate that these variables are factors that influence the decision to take LTP-HRT are summarized in Table 2.3.4. Prospective studies are underlined and studies that used a multivariate logistic regression analysis are in boldface. The specific covariates that are found to contribute to the decision-making process as outlined in the objectives of this thesis will be discussed in greater detail in the discussion section.

Table 2.3.4. Inputs in Decision-Making about HRT

Variables	†	Current/past vs never	Current vs never	Current vs past/never
Sociodemographic and Clinical Characteristics				
Patient Characteristics				
Younger Age	+	66 67	54 58 60(+-)52 76	98 57 65 53
	-	56	59	63 75
	ϕ	99(-) 68	48 74 104	55 64 69 70 71
Higher Education	+	50 66 67 99(-)	54 58 60(+-)52 104	98 75 69 70 71
	-		59	
	ϕ	92 56 103 51 68 72	74 76 61	55 57 64 65 107 53
Married or Common-law	+	50	54 58 74(-)	98
	ϕ	67 68	59 60(+-) 74(+) 76 104 61	55 57 62 65 69
Caucasian race	+	51 68	58 104	63 64 69 70
	-			98
	ϕ	73 72	54	55 71
Employed	+	80	61	
	ϕ	56 99(-)	52 104	55 65 69 70 71
Higher income	+	50 66	58	
	ϕ	68	76	57
occupation	+	50 103 80		
	ϕ		52	71
Urban residence	+		58	
	-		59	63
	ϕ	56		
Recent last menstrual period	+			64
	ϕ	99(-)	54	69
Have you had children	+	58 50	59 52	
	-	67		
	ϕ		60(+-) 77(+-)	62 53 69
Previous oral contraceptive use	+	92 51 99(-)	59 74	107 53
	ϕ	56 49 80	77(+-)	55 62
Hysterectomy	+	56 49 50 51 80 66 68 79	54 59 60 61	55 98 57 62 64 65 69 71
	ϕ	67 72		107 53
Oophorectomy	+	51	54 77(+) 74(+)	62 65
	ϕ		61	64
Current smoker	+	58 53		
	-	50 66	76	98
	ϕ	49 51 67 99(-) 68	60(+-) 77(+-)52 48 74 104	55 57 62 63 64 65 75 100 69 71
Drinks alcohol	+	58 49 51	59 60(+-) 76	64 65 75 71
	ϕ	50 99(-)	52 48 74	62 69
Lower BMI	+	49 51 99(-)	59 60(+-)	65 75 100
	ϕ	50 66 67 68 53	48 74 76	98 62 63 64

Variables	†	Current/past vs never	Current vs never	Current vs past/never
History of hypertension	+		59	100
	-		77(-)	
	ϕ	49 51 66 99(-) 68	77(+)74 76	55 63 69 71
history of hypercholesterolemia	+			63
	ϕ	51 66 99(-)	76	
History of diabetes	-		77(-)	63
	ϕ	51 68	77(+) 76	55 100
Family history of heart disease	ϕ	99(-) 72	74	100 71
History of angina or heart attack	-		77(-)	
	ϕ		59 77(+)	55 63 100
History of osteoporosis	+		45 60(-)48	63
	ϕ	56 58 79	60(+) 77(+-)	55
Family history of breast cancer	-	72	77(+-)	62 64
	ϕ	56 99(-)	74	98
Abnormal breast biopsy	ϕ		74	
Migraine headaches	+		77(+-)	
Vascular thrombosis	ϕ		77(+-)	
High triglycerides	ϕ	99(-)		
History of cancer of the uterus	ϕ	72		
History of cancer of the ovaries	ϕ		77(+-)	
Self-reported health	+		54	
	ϕ	58 51		55 69
Preventive behaviours $	+	58 49 66	59 76	64 65
	ϕ	56 50 103 51 99(-)	52 48 74	55 62
Perception of the Decision				
Knowledge/Experience:	+		78	55 64
Importance of heart disease	ϕ	72		
Importance of osteoporosis	+	56 72 79		
Importance of side effects	-	72		
Importance of breast cancer	ϕ	72		
Importance of vasomotor	+	56 80 79	54 78 77(+) 61	63 64 48 65
(menopausal) sx	ϕ	49 50		107
Perception of Important Others				
Advice of physician	+	79 72 73	78	55
Opinions of significant others	+	80		
	-		54	
	ϕ	79	54	
Menopause treated medically	+	53 72 73	78	65
Duration of relationship	+	58 49	54 59 61	
	ϕ	68		
Shared decision making	ϕ			55
Evaluation of Decision				
satisfaction with role	+			55

Legend

† This column describes the relation of the correlation: + = the row factor is positively associated with the decision to take HRT; - = the row factor is negatively associated; ϕ = the row factor is not associated.

*The numbers correspond to the reference

Bold The analysis was multivariate usually logistic regression

Underlined The study was prospective

Italicized The study was a case-control
(+) Analysis only included women who have had a hysterectomy
(-) Analysis excluded women who have had a hysterectomy
(±) Analysis was stratified by hysterectomy status and the result was the same for both groups
$ Preventive behaviours include exercise, mammograms, calcium supplementation, and Pap smears)

The majority of studies published have assessed the sociodemographic and clinical characteristics of the patient as a predictor of the decision to take HRT. Many of these studies indicate that women who take HRT are young, better educated, married, caucasian, and have a higher income. Critics of observational studies have felt that the large benefits reported when women take HRT are because the women who select HRT are healthier and have better health promotion actions. Interestingly, when considering the decision and covariates that are associated with health outcomes, 2 studies showed that smokers were more likely to take HRT[53; 58] and 10 studies found women were more likely to take HRT if they drank alcohol[49; 51; 58-60; 64; 65; 71; 75; 76]. In 7 studies, positive preventive behaviours (generally defined as exercise, having mammograms, taking calcium, etc.) were correlated with HRT use[49; 58; 59; 64-66; 76].

Pertaining to the medical history of the patient, very few studies demonstrated a correlation with a specific medical condition and the decision to take HRT. Two studies showed that diabetics were less likely to take HRT[63; 77] and four studies found that a family history of breast cancer was sufficient to reject taking HRT[62; 64; 72; 77].

Very few studies evaluated covariates that were in the category of the perception of the decision as a predictor of the decision: three studies demonstrated that women with a better knowledge were more likely to take HRT[55; 64; 78]. In the category of the opinions of important others, 5 studies assessed the effect of the advice of the physician on the decision to take HRT. All of the studies demonstrated that the advice of the physician was an important predictor of the decision[55; 58; 72; 78; 79]. Only two studies evaluated the impact of important others such as family, friends, or media, with one showing a positive impact[80] and the other study showed showing a negative impact on the decision[54].

One study has evaluated covariates from the category of evaluation of the decision as a factor influencing the decision to take HRT. Leveille et al[55]. found that satisfaction with the amount of information received from the physician was not correlated with the decision to take HRT in a multivariate analysis.

Conclusions

This review demonstrates the complexity of trying to understand those determinants that are important in the decision to take HRT. There is homogeneity in the design of the studies that were evaluated. Also, previous users are often included in the studies and are grouped with the never-users of HRT or the current users. The determinants that are considered for evaluation vary from study to study. The decision-making process has not been studied as factor that may influence the decision.

2.4. Rationale for this Study

An RCT is currently underway to evaluate the impact of a decision aid (DA) versus a pamphlet on the effectiveness of changing the modifiable determinants of the decision to take LTP-HRT. O'Connor has proposed that a DA be used as a decision support intervention to prepare the patient and the physician for the decision-making process[4]. The Cochrane Collaboration defines a DA as an intervention designed to help people make specific and deliberative choices among options by providing (at the minimum) information on the options and outcomes relevant to the person's health status[81]. This definition excludes passive informed consent materials, educational interventions that are not geared to a specific decision, or interventions designed to promote compliance with a recommended option rather than a choice based of personal values[81]. The goal of the trial is to demonstrate that the DA is more effective than the pamphlet at improving knowledge, clarifying values, and presenting risks and benefits so that women have realistic expectations following making a decision.

A decision aid using an audio-tape for patients and practitioners for the decision of whether or not to take HRT has been developed by O'Connor et al. [82]. The acceptance of this DA by patients and its effect on decisional conflict of postmenopausal women making a hypothetical decision regarding HRT has already been studied [83]. Compared with the pamphlet group, the decision-aid group had statistically significant ($p < 0.05$) improvements in terms of realistic personal expectations of the benefits and risks, decisional conflict, and perceived acceptability of the intervention. The improvements in realistic expectations and acceptability of the DA were clinically significant as well. In the pamphlet group 46% of the group had realistic expectations and 56% found the pamphlet acceptable as compared to the decision aid group where 72% had realistic expectations and 70% found the decision aid acceptable. The change in the decision conflict scale was statistically significantly different but a 0.2 difference on a 5-point scale may not be clinically relevant. Levels of general knowledge about the main benefits and risks were comparable for the two interventions.

The Decision Support Framework identifies components that are important in the decision-making process. The DSF is an appropriate framework to use when considering LTP-HRT. LTP-HRT is a decision that requires careful deliberation because of the uncertain and/or value-sensitive nature of the benefits and risks.

The primary and secondary objectives of this thesis are to examine the decision made regarding LTP-HRT and, using the DSF, to evaluate which components are significant in identifying the factors that influence this decision. The final decision or the decision assessed 2 months after the counseling interview was the primary objective. This decision is the decision that is the most clinically relevant. Also this decision is often the only decision that is assessed when decisions are made. The decisions after reviewing the intervention and after the counseling interview are secondary objectives. Understanding the factors that influence a woman's decision to take LTP-HRT will help in understanding the decision-making process. This may aid in our ability to participate in the decision-making process by identifying areas that could be targeted for more education, improving the decision-making process with more counseling and identify areas where more research is needed. The other secondary objectives of this thesis are to examine the factors associated with being uncertain regarding the use of LTP-HRT as well identifying women who change their opinions regarding the use of LTP-HRT after having a counseling interview with the physician.

3. Methods

3.1. Data Source

The data analyzed for this thesis came from an on-going RCT that is evaluating the effectiveness of a DA compared to a pamphlet, in changing the modifiable determinants of the decision to take LTP-HRT. A subset of the database, 126 patients who had made a decision regarding the use of LTP-HRT, was used to develop the statistical models to evaluate the primary and secondary objectives. The statistical models developed for the primary and secondary objectives were evaluated using a validation subset of the dataset.

3.1.1. Description of the Randomized Controlled Trial of the Decision Aid

The data collected for the RCT was obtained from approximately 126 post-menopausal women recruited from the practices of twenty-five family physicians in the Ottawa area, with each physician recruiting up to five women. The family physicians were randomly selected from the Ottawa area. Physicians eligible for recruitment into the study fulfilled the following criteria: they had a primary responsibility for a well-defined general practice population, they were > 5 years since graduation from medical school, < 60 years of age, and were not a geographic full-time academic family physician. Women eligible for recruitment fulfilled the following criteria: 45 to 69 years of age, postmenopausal for at least 1 year, able to read English, had never used HRT, had no history of osteoporosis-associated fractures, and had no absolute contra-indications to HRT (i.e., breast cancer, active liver disease, active vascular thrombosis, or unexplained vaginal bleeding). The family physician was randomized to use either the DA or the pamphlet produced by the ACP on LTP-HRT in the counseling interview. Therefore all women recruited by their family physician received the same decision support intervention.

3.1.2. Variable Selection for the Development of the Statistical Models

The Decision Support Framework (Figure 1) presents the variables, in boldface, that were evaluated for inclusion in the proposed statistical models. The variables for the study were collected at four time periods as illustrated in Figure 2: time 0 (T0) is the baseline data collection period, time 1 (T1) is the data collection period within 24 hours of reviewing the decision support intervention, time 2 (T2) is the data collection period within 24 hours of the counseling visit with the physician, and time three (T3) is the data collection period approximately two months after the physician visit.

Figure 2: Schematic Diagram of the Decision to Take LTP-HRT at the Various Time Periods

Time Periods	T0	T1	T2	T3
	Baseline	After Decision Intervention	After Counseling Interview	Two month Follow-up Visit
Objectives				
Primary Objective	*		*	✓
Secondary Objective 1a/b	*	* ✓		
Secondary Objective 2a/b	*		* ✓	
Secondary Objective 3	*	* Δ		
Outcomes				
No	52†	52	57	94
Unsure	58	49	34	3
Yes	16	25	34	29
Change	No		84	
	Yes		42	

* The time at which the variables used in the prediction were measured
✓ The time at which the outcome was measured for Primary Objective and Secondary Objective 1 and 2
Δ Indicates Secondary Objective 3 was measured as a change in opinion from T1 to T2
† Number of patients with the indicated decision at the various time points
a comparison of women who decision yes versus no
b comparison of women who were uncertain versus certain (yes and no combined)

The data collected at T0 included the following determinants of the decision: first, the sociodemographic characteristics of the patient and the physician, the clinical history of the patient, and the results of two quality of life measures (MENQoL and SF-12); and second, the perception of the decision, as measured by the baseline knowledge of LTP-HRT, an assessment of the patient's expectations and how realistic they were, a measurement of personal values of the risk and benefits of LTP-HRT, and a measurement of decisional conflict using the decision conflict scale. The actual questions that were presented to the women and how the data was calculated is presented in Appendix 2.

Each woman and her physician received the same decision support intervention. Within 24 hours of completing the intervention (T1), the perception of the decision as defined in the DSF was measured again. Then the patient had a counseling visit with her physician to discuss LTP-HRT. Within 24 hours of this visit (T2), the same variables as measured at T1 were measured again. As well, the decision as measured by the decision satisfaction scale was evaluated and the perception of important others, in particular the physician, was measured as well as the characteristics of the patient-physician relationship. Two months after the physician visit, all the patients were contacted (T3) for the results of their final decision.

3.1.3. Analytical Complexities of the Sample Design

Cluster or group randomization is frequently employed in the evaluation of health care, educational interventions, and screening strategies, since the randomization of individuals is undesirable or unfeasible[84; 85]. For example, it may be easier to recruit patients if the logistical and/or ethical problems of treating patients differently in a medical practice or worksite can be avoided[85; 86]. Cluster randomization may also serve to avoid treatment group contamination that might occur if subjects receiving different interventions are in close proximity or if the provider was familiar with both interventions[85; 86].

A disadvantage of cluster randomization is that the responses within a cluster are likely to be correlated with one another[84]. Unless the intracluster correlation that results from the sampling design is accounted for in the statistical analysis, the standard errors of the parameter estimates will be biased, usually in a way that exaggerates the statistical significance of the parameter [87]. The analysis must take into account intracluster correlation that could be present in the data[88]. Intracluster correlation is defined as the correlation between observations of the same cluster[89].

It is well known that standard statistical techniques cannot be directly applied to such data, since the usual assumption of independence among the sample observations is not satisfied [86]. When the outcome variable is dichotomous, the analytic challenges are particularly difficult, as virtually all of the methods that have been developed are approximations. One method of dealing with cluster designs is matching of experimental units on characteristics potentially related to the outcome in order to reduce confounding or to stratify on potential confounders[86]. However, these approaches become unwieldy as the number of confounders increase [86].

Cluster randomization for the study was chosen to prevent contamination from the physician. If the physician was exposed to both interventions and preferred one over the other, bias could be introduced into the counseling encounter. Thus all the inherent difficulties of this type of design need to be addressed for the analysis of the data.

3.2. Modeling

The two methodological issues arising in the analysis of the data from the RCT are analyzing the relationship of covariates to a dichotomous response and accounting for the correlation among subjects clustered within sampling units. The first issue is well established with ordinary logistic regression (OLR). OLR is a commonly employed statistical method to assess the relationship between the dichotomous outcome and covariates that includes both categorical and continuous variables[90]. The basic assumption of all regression analysis is that all observations are statistically independent, or at least uncorrelated with each other [84]. Statistical methods have recently been developed to account for the correlation among subjects. One method developed for analysis of correlated data is generalized estimating equations (GEE), which is an extension of generalized linear models (GLM). GEE can accommodate large numbers of clusters of varying sizes and is used to fit a broad range of models including loglinear and logistic models for correlated poisson, binary, and multinomial outcomes[90]. The following sections will review OLR, GLM, and GEE.

3.2.1. Review of Ordinary Logistic Regression

Logistic regression is used to describe the relationship between a categorical response variable and a set of explanatory variables that may include both categorical and continuous variables[90]. OLR remains a widely used and effective tool for assessing the magnitude of the effect of the explanatory variables on response probabilities.

Let the response variable, $y_i = 1$, with probability, π_i, for the ith individual if the outcome of interest is observed, and 0 otherwise. Also suppose that all individual's responses are statistically independent and that π_i may depend on a set of p explanatory variables, $x_{i1},\ldots,x_{ip}$, through an unknown regression px1 parameter vector, $\beta = (\beta_1,\ldots,\beta_p)'$, and γ, an intercept parameter for a reference population. To show this dependence, write $\pi_i(\beta_A)$, where $\beta_A = (\gamma,\beta)$ is the augmented parameter vector that includes the intercept. The joint distribution of the y_i, where $i = 1,\ldots, N$, where N is the number of subjects is

$$\prod_{i=1}^{N} \pi(\beta_A)^{y_i}[1-\pi_i(\beta_A)]^{1-y_i}. \qquad (1)$$

Viewed as a function of the unknown β_A with the data fixed, the above equation is the likelihood function. The logistic model for π_i is

$$\operatorname{logit}(\pi_i) = \log\frac{\pi_i}{1-\pi_i} = \eta_i = \gamma + x_i'\beta, \qquad (2)$$

where η_i is called the linear predictor and $x_i'\beta$ is notation for $\beta_1 x_{i1}+\ldots+\beta_p x_{ip}$. The odds ratio of a positive response for a unit increase in x_k is $\exp(\beta_k)$. The maximum likelihood estimate of $\hat{\beta}_A = (\hat{\gamma},\hat{\beta}_1,\ldots,\hat{\beta}_p)$ is obtained by substituting (2) into formula (1) and differentiating with respect to β_A to obtain the likelihood score equations

$$\sum_{i=1}^{N} x_{Ai}[(y_i - \pi_i(\beta_A)] = 0, \tag{3}$$

where $x'_{Ai} = (1, x_{i1}, \ldots, x_{ip})$, is the augmented covariate vector for the ith individual. The solution to equation 3 requires iteration since it is nonlinear in β_A. For sufficiently large samples, $\vec{\beta}_A$ has an approximate multivariate normal distribution. Inverting the Fisher information matrix yields the covariance matrix for $\vec{\beta}_A$ from which standard errors are extracted to construct confidence intervals for the true parameters β_k, or tests of significance based on Wald tests.

3.2.2. Review of Generalized Linear Models

GLM provides a common framework for analyzing regression models without making strict distribution assumptions. They have been applied to a variety of outcomes, including continuous, binary, categorical, and time-to-event[87]. GLM are a general class of models for independent observations[90]. A GLM has three components. First, a random component that defines the form of the distribution for the ith observation belonging to the exponential family of distributions. This family includes, the binomial, poisson, and normal distribution, corresponding to logistic, loglinear, and linear regression, respectively. Second, the systematic component given by the linear predictor, $\eta_i = x'_{Ai}\beta_A$, for the ith observation. Third, the link function, $g(\cdot)$, which links the random and systematic equations by the equation, $\eta_i = g(\mu_i)$. The general case for the marginal distribution of y_i has mean, variance, and the link function

$$E(y_i) = \mu_i, \qquad var(y_i) = v(\mu_i)\phi, \qquad g(\mu_i) = \eta_i = \gamma + x'_i\beta,$$

where $v(\cdot)$ is the variance function, γ is the intercept, β is a p x 1 vector of regression coefficients, and ϕ is the scale parameter. The regression coefficients, β_A, are estimated by solving the maximum likelihood score equations for β_A:

$$\sum_{i=1}^{N} D'_i \, var(y_i)^{-1}(y_i - \mu_i(\beta_A)) = 0, \tag{4}$$

where $D_i = \partial\mu_i / \partial\beta_A$.

For the logistic regression model, the mean, variance, and link function are specified as follows, $\mu_i = \pi_i, v(\mu_i) = \mu_i(1-\mu_i)$, and $g(\mu_i) = \log(\mu_i/(1-\mu_i))$. The scale parameter $\phi = 1$.

3.2.3. Review of Generalized Estimating Equations

Both OLR and GLM make the assumption that observations were independent. In many binary and categorical data situations, independence assumptions may not hold, and ignoring the intracluster correlation would lead to incorrect variance estimates of the regression parameters[90]. GEE may be viewed as an extension of GLM from random sampling to cluster sampling as GEE accounts for the dependence of observations within clusters[90]. The basic GEE method, referred to as GEE-independent, yields estimated regression coefficients computed as if the data were independent observations and applies a consistent variance that explicitly accounts for the within-cluster correlation[87].

Notation and general theory for GEE is presented using the specific application to OLR[87; 90]. Let n_i equal the number of observations in the ith cluster, and let K be the total number of clusters of possibly varying size. Clusters are indexed by i and observations are indexed by j. Let $y_i = (y_{i1}, \ldots, y_{in_i})'$ be a vector of outcome values for the n_i observations in the ith cluster. Then $x_i = (x_{i1}, \ldots, x_{in_i})'$ will be a vector for a single explanatory variable corresponding to these observations. For p explanatory variables then

$$X_i = \begin{bmatrix} x_{i11} & \mathrm{L} & x_{i1p} \\ \mathrm{M} & & \mathrm{M} \\ x_{in_i1} & \mathrm{L} & x_{in_ip} \end{bmatrix}$$

will be a $n_i \times p$ matrix of cluster-and/or observation-level covariate values where i is the number of clusters, j is the number of observations in the cluster, and p is the number of explanatory variables.

The first step is to describe the variance of y_{ij}. Let A_i be a diagonal matrix with diagonal elements equal to the variance of individual observations within the cluster $\text{Var}(y_{i1}),\ldots,\text{Var}(y_{in_i})$. Recall from the OLR model the mean and variance of the jth binary response to the ith cluster is given by

$$E(y_{ij}) = \Pr(y_{ij}) = \pi_{ij}, \quad \text{logit}(\pi_{ij}) = \eta_{ij} = \gamma + x_{ij}'\beta, \qquad v(\pi_{ij}) = \pi_{ij}(1-\pi_{ij}),$$

where $v(\pi_{ij})$ is the variance of y_{ij}. Thus A_i is of dimension n_i x n_i, where n_i is the number of observations in cluster i.

The next step in estimating the regression coefficients is to choose the form of a working correlation matrix $R(\alpha)$ to describe the within-cluster correlation, where α represents the unknown parameters associated with a specified model for the pairwise correlations. For the GEE-independent method, $R(\alpha)$ is the identity matrix. For other GEE methods, $R(\alpha)$ is more complex. Although the identity matrix specifies zero correlation among responses within a cluster for the GEE-independent method, estimates of the variance-covariance matrix of β are robust to mis-specification. Then, $V_i(\alpha) = A_i^{1/2}R_i(\alpha)A_i^{1/2}$ is the working covariance matrix for the vector of responses $y_i = (y_{i1},\ldots,y_{in_i})$ within each cluster i for the specific case of the GEE-independent method where $R(\alpha)$ is the identity matrix, and as a result $V_i = A_i$.

Having chosen an appropriate regression model, a variance function for individual observations y_{ij}, and an assumed form for the pairwise correlations between y_{ij} and y_{ij}, the estimating equations can be specified. Estimates of β_A are obtained by solving the GEE

$$U(\vec{\beta}_A) = \sum_{i=1}^{K} \frac{\partial \mu_i}{\partial \beta} V_i^{-1}(y_i - \mu_i(\beta_A)) = 0 \qquad (5)$$

where $\mu_i = (\mu_{i1},\ldots,\mu_{in_i})$ is the mean response vector for responses within a cluster, and $\frac{\partial \mu_i'}{\partial \beta}$ is the vector of first partial derivatives of the mean response μ_i with respect to the regression coefficients β_A. The covariance matrix is inserted to weight the data efficiently. The goal is to find the estimates of the regression coefficients that make $(y_i - \mu_i)$, the vector of the difference between observed and expected values, as small as possible. Iterative reweighted least squares are typically used to simultaneously solve the estimating equations. The GEE-independent method parameter estimates are asymptotically unbiased and normally distributed, regardless of the true correlation structure. Note the GEE-independent method parameter estimates are the same as those computed with the standard OLR models.

To account for the for the dependence of the observations within a cluster, Liang and Zeger[91] proposed a robust variance estimate for the estimated parameters:

$$V(\hat{\beta}_A) = M_0^{-1} M_1 M_0^{-1},$$

where

$$M_0 = \sum_{i=1}^{K} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$$

$$M_1 = \sum_{i=1}^{K} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1} (y_i - \mu_i)(y_i - \mu_i)' V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$$

This robust variance estimate consists of three terms and is often called the sandwich estimator. If the observations were independent, then M_0^{-1} would be an unbiased estimate of the variance of the regression coefficients. However, under cluster sampling, M_0^{-1} alone is sensitive to departures from the assumed correlation structure. The inclusion of the middle term M_1, serves as a variance correction when the correlation model has been incorrectly specified. It is a consistent variance estimate even when $R_i(\alpha)$ is not the true correlation matrix of y_i. For a large number of clusters, the GEE estimate of β_A has an approximate multivariate normal distribution. Thus, valid inference requires a sufficiently large sample size in terms of the number of clusters. Diagonal estimates are the variances of individual parameters, and off-diagonal elements are their estimated covariances. Similar to quasi-score expectations, the estimates of the regression coefficient vector depends on means and second moment parameters (variances and covariances) and does not require specification of the response vector's full multivariate distribution[90]. They extend quasi-likelihood by introducing additional parameters, α, to describe the nature of the intracluster correlation. However the power of statistical tests for β_A can be increased by carefully modeling $R_i(\alpha)$[90].

The GEE method maintains three statistical assumptions: 1) the model is linear; 2) the number of clusters is relatively large; and 3) the observations in different clusters are independent (i.e., that V_i is a block diagonal matrix). The following are advantages of the GEE method over other methods developed to analyze correlated data:

1) GEE estimates consistent standard errors in the presence of within-cluster correlation;
2) GEE provides a general framework that applies to nearly any kind of independent variable, including continuous, binary, categorical, and time-to-event;
3) The method does not make strict distributional assumptions (e.g., normality);
4) GEE is relatively simple to apply in practice through readily available software; and
5) GEE is suited for analyzing large numbers of clusters of varying size[87; 90].

The GEE-exchangeable method models the correlation structure within clusters[87]. The GEE-exchangeable method differs from the GEE-independent in the type of correlation matrix specified and in iterating between estimating the regression parameters and the correlations. The exchangeable correlation matrix signifies equal correlations among all pairs of responses within a cluster. The iterative estimation process results in parameter estimates that are not equal to the OLR results. Studies have shown that modeling the correlation structure explicitly can be more efficient then the GEE-independent method for estimating the effect of within-cluster covariates (e.g. gender, race, and age), particularly when the pairwise correlations are high. However, the GEE-exchangeable and GEE-independent methods have similar efficiency for between cluster covariates. Therefore if the study is more interested on the treatment effect, then the individual response the GEE-independent method may be used[87].

3.3. Analytical Methods

3.3.1. Development of Models

3.3.1.1. Description of Outcome Variables

Data from the first 126 patients from the RCT and their associated physicians were used to develop the following statistical models. The dependent variable for the primary objective was the final decision made (yes or no) regarding the usage of LTP-HRT at the follow-up assessment (T3). Any women who had not made a decision regarding LTP-HRT at this point were excluded to ensure that only those who had made a firm decision at this point were considered.

For the secondary objective 1, the dependent variable is the preference to take LTP-HRT after reviewing the intervention (T1). For the secondary objective 2, the dependent variable is the initial decision to take LTP-HRT after the physician visit (T2). For both secondary objectives 1 and 2, the dependent variable had three possible outcomes, 'no', 'yes', or 'unsure' (Figure 2). Both of these objectives were analyzed by re-categorizing the outcome variables into dichotomous response variables. First, all women who were uncertain were excluded; the possible responses to the preference of initial decision to take LTP-HRT was then 'yes' or 'no'. This analysis was referred to as Secondary Objective 1a and 2a. Second, the women who were uncertain were compared to the women who were certain, (i.e. either for or against LTP-HRT). This analysis was referred to as Secondary Objective 1b and 2b for the preference and initial decision respectively.

For the secondary objective 3, the women whose preference after reviewing the intervention (T1) was different from their initial decision after the counseling visit (T2) were compared to those whose preference did not change.

3.3.1.2. Univariate Analysis

The statistical program used for the univariate analysis was SPSS© v 8.0. The univariate relationships between each available covariate from the Decision Support Framework and each outcome variable were examined. For continuous variables the student's t-test was used and chi-square (χ^2) was used for categorical variables. The variables that appeared to be related to the outcome ($p < 0.10$) were considered for inclusion in the model. A p-value of 0.10 was used for this analysis to keep the number of covariates considered for inclusion in the statistical models at a reasonable number. For each covariate, the physician level cluster may interfere with the independence of the observations. A stratified univariate analysis between each outcome variable and covariate adjusting for the correlation due to the physician cluster was examined. This analysis used the GEE model with the decision as the outcome variable and the covariate as the independent variable. Any covariates that reached a significance of $p<0.10$ were also considered for inclusion in the model.

3.3.1.3. Multivariate analysis

All multivariable analysis was performed using SAS© v7. For each covariate, the physician level cluster may interfere with the independence of the observations. The physician level cluster was accounted for in the model development stage using GEE in two ways.

a) For each objective an OLR model was developed using PROC LOGISTIC based on a forward stepwise method using the log-likelihood difference between two models with and without the addition or removal of a covariate to the model. A significance level of 0.05 was used for addition and removal of covariates. The variables that were included in the OLR model were entered into a GEE model using PROC GENMOD. This method will be referred to as GEE.

b) For each objective a GEE model was developed using a forward stepwise method analogous to the OLR method with a significance level of 0.05 for addition and removal of covariates. This method will be referred to as GEE Stepwise.

The intervention was an important design variable so it was included as a covariate in all models. Model development was performed using hierarchical model building.

Collinearity among the predictor variables is a problem with multivariate analysis as they provide redundant information[92]. This redundancy confounds attempts to identify the individual contributions and relative merits of the predictor variables[93]. Possible collinearity was identified based on clinical experience and the covariates considered were the physical subscales of the SF-12 and the MENQoL and the decision conflict scale and its subscales. Both the SF-12 and the MENQoL had physical subscales. The SF-12 assessed distress from physical symptoms in general and the MENQoL addressed distress from physical symptoms that were related to the postmenopausal period. The DCS was developed as a total scale and separate subscales. If both the total scale and a specific subscale were used in a model redundant information could be included. Significant collinearity is unlikely between subscales, as collinearity was assessed in scale development. As a hierarchical model building strategy was utilized, if both covariates entered the model in the stepwise procedure, the variable that was added first (had a more significant contribution) was retained in the model.

All first-order interactions that had been identified in previous studies were considered for inclusion in the model if both of the base terms were included in the model. This included hysterectomy status with the age of the women as well as the number of years since the last menstrual period[50; 59] and hysterectomy status and the advice of the health care professional[49]. First-order interactions between the decision support intervention and each covariate included in the models was also assessed. The design of the primary study had been to demonstrate that the decision aid was a more effective intervention than the pamphlet at changing the modifiable determinants of the decision. It is conceivable that this important design variable may have significant interactions with covariates in the Decision Support Framework.

The GENMOD procedure has the capability of performing a stepwise analysis, called a Type 3 analysis, to assess the contribution of covariates[94]. A Type 3 analysis consists of defining an estimable function for an effect of interest. Then maximum likelihood estimation is performed under the constraint that the Type 3 function of the parameters is equal to 0. If the resulting constrained parameter estimates is $\overset{:}{\beta}$ and the log likelihood is $l(\bullet)$, then the likelihood ratio statistic

$$S = 2(l(\hat{\beta}) - l(\overset{:}{\beta}))$$

where $\hat{\beta}$ is the unconstrained estimate, has an asymptotic chi-square distribution under the hypothesis that the Type 3 contrast is equal to 0 and with degrees of freedom equal to the number of parameters associated with the effect. For a Type 3 analysis, PROC GENMOD produces the likelihood ratio statistics, degrees of freedom, and p-values based on the limiting chi-square distributions for each effect in the model. The results of this type of analysis do not depend on the order in which the terms are specified in the MODEL statement. Thus, a Type 3 analysis can be used to add and remove variables in a fashion analogous to the forward stepwise procedure for OLR.

3.3.1.4. Review of models

The variables that were included in the models were reviewed for contribution to the prediction ability of each model. The test statistics used to test the models was the Hosmer and Lemeshow Goodness of Fit statistic[95]. Also, the models were tested for overdispersion. Overdispersion is essentially overfitting of the model. With an overfitted model the risk estimates may be unreliable if the multivariate data contain too few outcome events relative to the number of independent variables[96]. Overdispersion was tested for in two ways. First, in multivariate model development it is generally accepted that there must be at least 10 outcome events for each covariate[97]. Second, a shrinkage coefficient was used to quantify overfitting[97]. The heuristic shrinkage estimator of van Houwelingen and le Cessie was used, namely

$$\hat{\gamma} = \frac{\text{model } \chi^2 - p}{\text{model } \chi^2}$$

where p is the number of regression parameters (excluding any intercept(s) but including all non-linear and interaction effects) and the model χ^2 is the total likelihood ratio χ^2 statistic (computed using the full set of p parameters) for testing whether any predictors are associated with the outcome variable. A shrinkage coefficient less than 0.85 demonstrates overdispersion. Therefore, when the number of covariates in the model exceeded 10 outcome events for each covariate, the covariate that had the least significant contribution to the predictability of the model was dropped to limit overdispersion. This step was repeated until there were at least 10 outcome events for each covariate in the model, the Hosmer and Lemeshow test was not significant, and the shrinkage statistic was greater than 0.85. The decision intervention was counted as one of the covariates when determining if there were 10 outcome events for each covariate in the model.

3.3.1.5. Interpretation of the Models

The final multivariate model will include the intervention, the significant factors, and the interactions that predict the outcome. Each variable in the model will be adjusted for the other variables included in the model as well as for the physician cluster. The model can be applied to a woman to predict the outcome of interest.

The coefficients of the variables in the model can be expressed as odds ratios. In a RCT, the odds ratio compares the odds of an event in the treated group with the odds in the control group. In this study, the odds ratio compares the odds of a positive outcome as defined by the study objective (for example, the final decision is to take LTP-HRT), in the presence of the covariate as compared to the absence of the covariate (for example, the covariate is hysterectomy status). The multivariate modeling techniques yield odds ratios for each covariate. The group that does not have the covariate is not a control group and thus the more familiar risk ratio (relative risk) cannot be reported. Relative risk expresses the relative probability that an event will occur when two groups are compared. Risk ratios and odds ratios are similar when the incidence of the event in the control group is rare (less than 10%). The odds ratio is always further from unity than the risk ratio, thereby apparently magnifying the treatment effect[92].

3.3.2. Reproducibility of the Models

After the final model was developed, an evaluation of its reproducibility was performed. The final models for the various objectives were applied to the next 55 patients that were enrolled in the RCT. Physician data is still pending on approximately half of this dataset. The Hosmer and Lemeshow test was used to assess the goodness of fit of the model.

4. Results

4.1. Descriptive Statistics of Development and Validation Dataset

The development set included 126 patients distributed among 31 physicians. The number of patients by physician ranged from a minimum of 1 to a maximum of 5 patients. Sixteen physicians with their 74 patients were randomized to the decision aid group and 15 physicians and their 52 patients were randomized to the pamphlet group. Table 4.1 displays the characteristics that were measured at the patient level, the time periods in which they were measured, means and standard deviations for the characteristics that were continuous and percentages for the characteristics that were categorical. The characteristics are categorized in the table according to the DSF. The categories of the DSF are the sociodemographic characteristics of the patient and the physician, the measures of the perception of the decision, the perception of the physician, and the evaluation of the decision.

Table 4.1.Variables from the Decision Support Framework (all patients, n=126)

Variable name	Baseline	T1	T2	T3
Design				
Intervention %DA	58.7*			
Patient Characteristics				
Age (years)	55.6 (6.3)†			
Employed (%working)	57.1			
Education (%some post secondary)	68.3			
Hysterectomy	27.8			
Last Menstrual Period (years)	9.0 (7.2)			
Coronary Heart Disease	4.8			
Hypertension	24.6			
Diabetes	4.0			
High Cholesterol	25.4			
High Triglycerides	6.3			
Fibroids	18.3			
Smoker (%current)	11.1			
FHx of Heart Disease	32.5			
FHx of Breast Cancer	15.9			
MENQoL Vasomotor subscale	2.8 (1.9)			2.3 (1.6)
MENQoL Psychosocial subscale	3.0 (1.6)			2.7 (1.5)
MENQoL Physical subscale	3.3 (1.3)			2.7 (1.2)
MENQoL Sexual subscale	2.5 (1.9)			2.0 (1.5)
SF12 Physical subscale	26.3 (5.8)			26.4 (5.4)
SF12 Mental subscale	51.9 (7.0)			53.3 (6.6)
Physician Characteristics				
Satisfaction with autonomy	79.4			
Year of Graduation >1978	50.8			
Av. No. patients/week >120	40.5			
Gender female	46.8			
CCFP	71.4			
Perception of the Decision				
Knowledge	50.0 (21.4)	79.1 (16.6)	76.7 (17.5)	
Realistic Expectations	25.2 (16.2)	34.2 (20.3)	32.2 (22.5)	
Value of Heart Disease	7.8 (3.0)	7.7 (2.8)	7.5 (2.8)	
Value of Osteoporosis	8.0 (2.6)	7.1 (2.9)	7.1 (2.9)	
Value of Side Effects	9.0 (1.8)	7.7 (2.7)	7.9 (2.4)	
Value of Breast Cancer	8.7 (2.3)	8.3 (2.5)	8.2 (2.5)	
DCS Total	2.8 (0.7)	2.4 (0.6)	2.1 (0.6)	
Uncertainty subscale	3.1 (1.2)	3.0 (1.1)	2.6 (1.0)	
Knowledge subscale	2.9 (1.0)	2.1 (0.6)	1.9 (0.6)	
Supported subscale	2.5 (0.6)	2.2 (0.6)	2.0 (0.6)	
Values subscale	2.8 (1.0)	2.2 (0.7)	2.0 (0.6)	
Satisfaction subscale	2.4 (0.6)	2.3 (0.7)	2.0 (0.7)	
Perception of the Decision				
Length relationship (% >5 years)	54.8			
Patient decision role (%change)			46.8	
Doctor would prescribe HRT			51.6	
Evaluation of Decision				
Satisfaction with decision			11.3(2.0)	11.3 (2.1)
Satisfaction with process			46.8 (7.5)	46.9 (7.4)

* categorical variables are presented as percentages † continuous variables are presented as means and standard deviations

The average age of the patients was 55.6 years. The majority of women were well educated with 68.3% of the women having at least some postsecondary education and 57.1% were currently employed outside of the home. For the women's past medical history, 27.8% of the women had had a hysterectomy and the most common medical conditions were hypertension and high cholesterol in 24.6% and 25.4% of the sample respectively. As for the physicians, there were slightly fewer females than males (46.8%), the average year of graduation from medical school was 1979, and the majority of the physicians were certified by the Canadian College of Family Physicians (71.4%). The majority of the patients (54.8%) had been with their family doctor for greater than 5 years.

Figure 2 illustrates the four time periods in the study and the number of patients responding for each outcome for each objective at the specified time periods. The model results will be described in the order of occurrence of the decision to take or consider taking LTP-HRT as outlined in Figure 2. The models that are predicting the decision will be presented first and then the models that are predicting the uncertain group or the change in opinion.

The models that were developed were tested for reproducibility using the next consecutive 55 patients from the RCT. The descriptive statistics for this group are presented in Table 4.1.1. The only notable difference between the development set and the validation set is fewer women in the validation set were randomized to the decision aid. This resulted from the fact that the RCT had a different dropout rate from the two groups, with more physicians randomized to the pamphlet withdrawing. The randomization was restructured to rebalance the groups for the RCT.

Table 4.1.1 Variables from the Decision Support Framework (validation set, n=55)

Variable name	Baseline	T1	T2	T3
Design				
Intervention %DA	41.8*			
Patient Characteristics				
Age (years)	54.1 (4.3)†			
Employed (%working)	80.0			
Education (%some post secondary)	70.9			
Hysterectomy	11.1			
Last Menstrual Period (years)	5.7 (5.4)			
Coronary Heart Disease	0.0			
Hypertension	14.5			
Diabetes	7.3			
High Cholesterol	18.2			
High Triglycerides	1.8			
Fibroids	12.7			
Smoker (%current)	5.5			
FHx of Heart Disease	21.8			
FHx of Breast Cancer	9.1			
MENQoL Vasomotor subscale	3.3 (1.9)			2.2 (1.5)
MENQoL Psychosocial subscale	3.5 (1.8)			2.7 (1.5)
MENQoL Physical subscale	3.5 (1.5)			2.6 (1.3)
MENQoL Sexual subscale	2.9 (2.0)			2.3 (1.7)
SF12 Physical subscale	26.6 (6.0)			25.5 (4.5)
SF12 Mental subscale	52.0 (6.8)			54.5 (4.9)
Physician Characteristics				
Satisfaction with autonomy	90.2			
Year of Graduation >1978	58.5			
Av. No. patients/week >120	39.2			
Gender female	42.9			
CCFP	61.8			
Perception of the Decision				
Knowledge	50.4 (20.5)	78.9 (16.2)	76.5 (15.0)	
Realistic Expectations	22.8 (18.7)	28.9 (21.1)	31.0 (22.7)	
Value of Heart Disease	7.5 (2.6)	7.0 (2.6)	7.3 (2.5)	
Value of Osteoporosis	7.7 (2.7)	7.2 (2.7)	7.6 (2.6)	
Value of Side Effects	9.0 (1.3)	7.9 (2.3)	7.8 (2.1)	
Value of Breast Cancer	9.1 (1.5)	8.2 (2.2)	8.1 (2.2)	
DCS Total	2.9 (0.6)	2.5 (0.4)	2.2 (0.5)	
Uncertainty subscale	3.4 (0.9)	3.1 (1.0)	2.7 (0.9)	
Knowledge subscale	2.9 (0.9)	2.2 (0.6)		
Supported subscale	2.6 (0.6)	2.4 (0.5)		
Values subscale	2.9 (0.8)	2.3 (0.6)	2.0 (0.5)	
Satisfaction subscale	2.7 (0.7)	2.5 (0.5)	2.2(0.5)	
Perception of the Decision				
Length relationship (% >5 years)	60.0			
Patient decision role (%change)			58.2	
Doctor would prescribe HRT			53.1	
Evaluation of Decision				
Satisfaction with decision			11.3 (1.7)	11.0 (1.7)
Satisfaction with process			46.9 (6.6)	45.5 (7.2)

* categorical variables are presented as percentages † continuous variables are presented as means and standard deviations

4.2. Description of Models

4.2.1. Preference after the Decision Intervention (Secondary Objective 1a)

4.2.1.1. Univariate Analysis of Secondary Objective 1a

The variables that were significantly related to the preference to take LTP-HRT after the intervention (T1) by the univariate and adjusted univariate analysis are presented in Table 4.2.1.1. Women were more likely to prefer LTP-HRT if they were younger, less educated, had a hysterectomy, a positive history of high cholesterol, triglycerides, or fibroids, had a family history of early heart disease, and had no family history of breast cancer. All subscales of the MENQoL were higher (i.e., experiencing more symptoms) and the physical subscale of the SF-12 was higher in women who preferred LTP-HRT. Women who placed a higher value on the importance of heart disease and osteoporosis and a lower value on the importance of side effects and breast cancer were more likely to prefer LTP-HRT.

Table 4.2.1.1. Univariate Analysis for Preference towards LTP-HRT after the Decision Intervention (Secondary Objective 1a)

Variable name	No (n=52)	Yes (n=25)	p-value^	p-value‡
Design				
Intervention % DA§	61.5*	60.0	0.897	0.604
Patient Characteristics				
Age	56.5 (6.4)†	53.5 (4.7)	0.042	0.456
Education – some postsecondary	73.1	60.0	0.246	0.000
Hysterectomy	15.4	48.0	0.002	0.001
Hypertension	15.4	36.0	0.041	0.150
High Cholesterol	15.4	36.0	0.041	0.443
High Triglycerides	1.9	12.0	0.062	0.030
Fibroids	11.5	28.0	0.071	0.777
FHx of early Heart Disease	26.9	56.0	0.013	0.322
FHx of Breast Cancer	28.8	8.0	0.039	0.405
MENQoL Psychosocial subscale	2.7 (1.5)	3.9 (1.3)	0.013	0.427
MENQoL Physical subscale	2.2 (1.6)	3.4 (2.4)	0.000	0.126
MENQoL Sexual subscale	2.2 (1.6)	3.4 (2.4)	0.016	0.169
SF-12 Physical subscale	25.6 (6.0)	29.2 (4.9)	0.013	0.228
Perception of the Decision				
Heart Disease	6.0 (3.0)	9.2 (1.7)	0.000	0.010
Osteoporosis	6.0 (3.0)	7.4 (2.8)	0.074	0.002
Side Effects	8.3 (2.7)	6.6 (3.1)	0.019	0.567
Breast Cancer	8.7 (2.1)	6.4 (3.3)	0.000	0.090

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at p<0.10 for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.1.2. Model Development of Secondary Objective 1a

The models developed for this objective are outlined in Table 4.2.1.2. The GEE and GEE Stepwise resulted in the same model. Four variables were included in the model with a sample size of 77 with 25 positive outcome events and the shrinkage statistic for the model was 0.82. The reduced model, which did not include hysterectomy status, had a better shrinkage statistic (0.89) and the Hosmer and Lemeshow Goodness of Fit Statistic (HL) was 11.387 (p=0.18). The interpretation of the parameters for the full model is as follows. For each one unit increase on a ten point scale measuring the importance of heart disease, the odds were 2.5:1 (95% confidence interval (CI): 1.6, 4.0) that they would prefer LTP-HRT. For each one unit increase on a ten point scale measuring the importance of breast cancer, the odds were 0.5:1 (95% CI: 0.4, 0.7) that they would prefer

LTP-HRT or 2:1 that they would not prefer LTP-HRT. For women who had a hysterectomy, the odds were 11.6:1 (95% CI: 3.9, 34.5) that they would prefer LTP-HRT than those with a uterus.

Table 4.2.1.2. Models for Preference towards LTP-HRT after the Decision Intervention (Secondary Objective 1a)

Models*	OLR	GEE & GEE Stepwise	GEE Reduced
Variables	**OR(95% CI)**	**OR (95%) CI**	**OR (95%) CI**
Intervention	0.9 (0.2, 4.6)	**0.9 (0.2, 3.3)**	0.7 (0.2, 2.6)
Value of Heart disease	2.5 (1.6, 4.8)	**2.5 (1.6, 4.0)**	2.3 (1.2, 4.5)
Value of Breast Cancer	0.5 (0.3, 0.7)	**0.5 (0.4, 0.7)**	0.5 (0.4, 0.8)
Hysterectomy	11.9 (2.3, 87.8)	**11.6 (3.9, 34.5)**	
Model Statistics			
Hosmer and Lemeshow	1.620 (p=0.99)	**6.322 (p=0.61)**	11.387 (p=0.18)
Shrinkage	0.92	**0.82**	0.89
External Validation n=30		**10.867 (p=0.21)**	9.632 (p=0.29)

The Final Model is in the Column with Boldface
* The models are defined as:
OLR = The model was developed using Ordinary Logistic Regression
GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations
GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations
GEE Reduced = The model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10

4.2.1.3. Model Validation of Secondary Objective 1a

The data was validated using the dataset of 55 patients described in Section 3.3.2. After excluding unsure women, 30 patients remained of which 9 patients preferred LTP-HRT. The HL was 10.867 (p=0.21). The p-value is greater than 0.05 so it is not possible to prove that the model is not predicting the decision. Therefore, there is support that this model is a good fit and predicts the preference to take LTP-HRT after the reviewing the decision intervention.

4.2.2. Decision after the Counseling Interview (Secondary Objective 2a)

4.2.2.1. Univariate Analysis of Secondary Objective 2a

The variables that were significantly related to the initial decision to take LTP-HRT after the counseling interview by the univariate and adjusted univariate analysis are presented in Table 4.2.2.1. Women were more likely to initially decide to take LTP-HRT if they were of younger age, had a hysterectomy, a positive history of fibroids, had a family history of early heart disease, and had no family history of breast cancer. All subscales of the MENQoL were higher (i.e., experiencing more symptoms) and the physical subscale of the SF-12 was higher in women whose initial decision was to take LTP-HRT. Patients whose physician was male were more likely to have an initial decision to take LTP-HRT. Women whose initial decision was to take LTP-HRT placed a higher value on the importance of osteoporosis and heart disease and a lesser value on the importance of breast cancer. Women whose initial decision was to take LTP-HRT had a higher satisfaction with their decision and the decision making process. A number of variables became significant when an adjustment was made for the physician: the satisfaction subscale of the DCS; whether or not the physician held CCFP certification; and if the length of the patient-physician relationship was greater than 5 years.

Table 4.2.2.1. Univariate Analysis for the Decision after the Counseling Interview (Secondary Objective 2a)

Variable name	No (n=57)	Yes (n=34)	p-value^	p-values‡
Design				
Intervention§	61.4*	52.9	0.428	0.9727
Patient Characteristics				
Age	56.4 (6.1)†	53.7 (5.2)	0.033	0.338
Hysterectomy	19.3	47.1	0.005	0.004
Fibroids	14.0	29.4	0.075	0.051
FHx of Heart Disease	24.6	44.1	0.053	0.043
FHx of Breast Cancer	28.1	5.9	0.010	0.100
MENQoL Vasomotor subscale	2.6 (1.7)	3.6 (2.2)	0.023	0.001
MENQoL Psychosocial subscale	2.8 (1.5)	3.7 (1.4)	0.005	0.046
MENQoL Physical subscale	3.0 (1.2)	3.8 (1.1)	0.001	0.001
MENQoL Sexual subscale	2.2 (1.7)	3.0 (2.1)	0.075	0.010
SF12 Physical subscale	24.6 (5.4)	28.7 (5.2)	0.001	0.014
Physician Characteristics				
Gender (%female)	50.9	32.4	0.085	0.008
CCFP (%yes)	73.7	70.6	0.749	0.000
Perception of the Decision				
Value of Heart Disease	6.3 (3.0)	7.8 (2.8)	0.000	0.645
Value of Osteoporosis	6.3 (3.0)	7.8 (2.8)	0.023	0.025
Value of Breast Cancer	8.5 (2.4)	7.4 (2.8)	0.043	0.036
DCS Satisfaction subscale	1.8 (0.6)	1.8 (0.5)	0.564	0.008
Perception of the Physician				
Length of relationship>5 years	56.4	52.9	0.672	0.000
Physician prescribe HRT	26.3	88.2	0.000	0.000
Evaluation of Decision				
Satisfaction with decision	12.3 (1.6)	11.3 (2.2)	0.016	0.028
Satisfaction with process	48.7 (7.2)	45.2 (8.2)	0.037	0.005

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at $p<0.10$ for the univariate or stratified univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.2.2. Model development of Secondary Objective 2a

The models developed for this objective are outlined in Table 4.2.2.2. The models developed by the GEE and GEE Stepwise included different variables. The first column of the GEE Stepwise includes both the physical subscale of the MENQoL and the physical subscale of the SF-12. Since these two variables are correlated (Pearson correlation is 0.323, $p<0.01$), the variable made the smaller contribution to the model was eliminated. Therefore the physical subscale of the SF-12 was eliminated from the stepwise procedure to decrease collinearity. The sample size for the development of these models was 91 with 34 positive outcome events. The GEE Stepwise model in the second column included five variables for only 34 positive outcome events, therefore the variable that was least statistically contributing was dropped to yield a model that will be referred to as GEE Reduced. For the GEE Reduced model the HL was 8.044 ($p=0.43$) and the shrinkage statistic was 0.88.

Table 4.2.2.2. Models for Decision after the Counseling Interview (Secondary Objective 2a)

Models	OLR	GEE	GEE Stepwise	GEE Reduced
Variables	**OR(95% CI)**	**OR (95%) CI**	**OR (95%) CI**	**OR (95%) CI**
Intervention	0.2 (0.0, 1.1)	0.4 (0.1, 1.5)	0.3 (0.1, 1.0)	0.3 (0.1, 0.9)
Physician prescribe HRT	155.5 (22.3, 999)	95.6 (17.1, 534.1)	64.6 (14.0, 299.4)	76.6 (13.8, 427.2)
MENQoL Physical subscale			2.1 (1.1, 3.9)	1.9 (1.1, 3.4)
SF12 Physical subscale	1.4 (1.2, 1.7)	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
MENQoL Vasomotor subscale				
History of Breast Cancer			0.2 (0.0, 0.9)	
Fibroids	11.5 (1.8, 130.8)	10.9 (2.2, 54.7)		
Interaction (IntxPhys*)				
Model Statistics				
Hosmer and Lemeshow	4.565 (p=0.80)	2.827 (p=0.94)	7.446 (p=0.49)	3.598 (p=0.90)
Shrinkage	0.94	0.87	0.82	0.87
External Validation n=33		33.364 (p<0.01)	47.352 (p<0.01)	82.910 (p<0.01)

Models	GEE Stepwise†	Gee Reduced†	GEE Reduced Int
Variables	**OR (95% CI)**	**OR (95%) CI**	**OR (95%) CI**
Intervention	0.2 (0.1, 0.8)	**0.3 (0.1, 1.0)**	17.7 (0.36, 867.7)
Physician prescribe HRT	73.3 (16.2, 332.9)	**62.0 (13.3, 289.7)**	88.8 (13.8, 569.5)
MENQoL Physical subscale	2.4 (1.3, 4.5)	**2.3 (1.3, 4.0)**	18.2 (2.05, 161.2)
SF12 Physical subscale			
MENQoL Vasomotor subscale	1.4 (1.1, 1.7)	**1.4 (1.1, 1.7)**	1.4 (1.1, 1.7)
History of Breast Cancer	0.1 (0.0, 0.9)		
Fibroids			
Interaction (**IntxPhys)			0.3 (0.1, 0.9)
Model Statistics			
Hosmer and Lemeshow	8.607 (p=0.38)	**8.044 (p=0.43)**	3.273 (p=0.92)
Shrinkage	0.84	**0.88**	0.83
External Validation n=33	16.127 (p=0.04)	**12.045 (p=0.15)**	65928 (p<0.01)

The Final Model is in the Column with Boldface
* The models are defined as:
OLR = The model was developed using Ordinary Logistic Regression
GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations
GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations
GEE Reduced = The model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10
GEE Reduced Int = The model included significant interactions
**IntxPhy is the interaction term between the intervention and the MENQoL physical subscale

Testing for significant interactions revealed an interaction between the intervention and the MENQoL physical subscale. The interaction term was not included in the model as there would be fewer than 10 outcome events for each covariate and the shrinkage coefficient was less than 0.85. Therefore the final model employed was the GEE Reduced model. The interpretation of the model parameters is as follows. If their physician would prescribe LTP-HRT, the odds were 62.0:1 (95% CI: 13.3, 289.7) that they would initially decide to take LTP-HRT. For each unit increase in the physical subscale of the MENQoL (more physical symptoms), the odds were 2.3:1 (95% CI: 1.3, 4.0) that they would initially decide to take LTP-HRT. For each unit increase in the vasomotor subscale of the MENQoL (more vasomotor symptoms), the odds were 1.4:1 (95% CI: 1.1, 1.7) that they would initially decide to take LTP-HRT.

4.2.2.3. Model Validation of the Secondary Objective 2a

The data was validated using the dataset of 55 patients described in Section 3.3.2. After excluding unsure women, 28 women remained of which 10 initially decided to take LTP-HRT. The HL was 12.045 (p=0.15). The p-value is greater than 0.05 so it is not possible to prove that the model is not predicting the decision. Therefore, there is support that this model is a good fit and predicts the initial decision to take LTP-HRT after the counseling interview.

4.2.3. Decision 2 months after the counseling interview (Primary Objective)

4.2.3.1. Univariate Analysis of Primary Objective

The variables that were significantly related to the final decision to take LTP-HRT at the follow-up visit by the univariate and adjusted univariate analysis are presented in Table 4.2.3.1. Women were more likely to decide to take LTP-HRT if they were of younger age, had a hysterectomy, had a family history of early heart disease, and had no family history of breast cancer. Patients whose final decision was to take LTP-HRT had higher scores on all subscales of the MENQoL (more symptoms of distress) as well as the physical subscale of the SF12. Of particular interest, female physicians were less likely to prescribe LTP-HRT. In the category of the perception of the decision, knowledge, realistic expectations, and the value of osteoporosis were not significant. Women more likely to take LTP-HRT had lower values on the overall decision conflict scale (less decision conflict), as well as the subscales for uncertainty (less uncertainty), values (clear values), and satisfaction (more satisfaction). The preference of the physician for the patient to take LTP-HRT was significant.

Table 4.2.3.1. Univariate Analysis for Decision Two Months after Counseling Interview (Primary Objective)

Variable name	No (n=94)	Yes (n=29)	p-value^	p-value‡
Design				
Intervention§	60.6*	55.2	0.600	0.874
Patient Characteristics				
Age	56.4(6.5) †	52.9 (4.5)	0.007	0.001
Hysterectomy	20.2	51.7	0.001	0.000
FHx of Heart Disease	25.5	58.6	0.001	0.000
FHx of Breast Cancer	20.2	3.4	0.032	0.062
MENQoL Vasomotor subscale	2.6 (1.7)	3.5 (2.3)	0.023	0.026
MENQoL Psychosocial subscale	2.7 (1.5)	4.0 (1.2)	0.000	0.001
MENQoL Physical subscale	3.1 (1.3)	4.0 (1.2)	0.001	0.003
MENQoL Sexual subscale	2.2 (1.7)	3.4 (2.3)	0.003	0.007
SF12-Physical subscale	25.6(5.7)	28.7 (5.6)	0.014	0.001
Physician Characteristics				
Gender %female	49.4	35.0	-	0.024
Perception of the Decision				
Value of Heart Disease	7.1 (2.9)	8.8 (2.2)	0.007	0.002
Value of Side Effects	8.0 (2.4)	7.3 (3.0)	0.141	0.004
Value of Breast Cancer	8.3 (2.4)	7.4 (3.0)	0.094	0.001
DCS Total	2.1 (0.6)	1.9 (0.5)	0.050	0.032
Uncertainty subscale	2.6 (1.0)	2.3 (.8)	0.119	0.021
Values subscale	2.1 (.6)	1.9 (.5)	0.082	0.038
Satisfaction subscale	2.1 (.7)	1.8 (.5)	0.091	0.056
Perception of the Physician				
Physician prescribe HRT	38.7	93.1	0.000	0.000

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at p<0.10 for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.3.2. Model Development of Primary Objective

The models developed for this objective are outlined in Table 4.2.3.2. The variables that were included in the GEE model were family history of heart disease, the psychological subscale of the MENQoL, the uncertainty subscale of the decision conflict scale, and the doctor's preference for the patient to take LTP-HRT. The GEE Stepwise procedure also included family history of breast cancer in addition to the variables included in the GEE model. Comparing the GEE model to the GEE Stepwise model, the addition of family history of breast cancer did not improve the HL (5.73 versus 6.35). Further, the shrinkage statistic decreased from 0.86 to 0.82 with the addition of the family history of breast cancer in the GEE Stepwise. As a result, family history of breast cancer was eliminated from the model. The final model is the GEE Reduced model which was the same as the GEE model. The interpretation of the model parameters is as follows. If a patient has a family history of heart disease the odds were 4.0:1 (95% CI: 1.4, 11.8) that they would make a final decision to take LTP-HRT. For each one unit increase in the psychological subscale of the MENQoL (more psychological distress), the odds were 2.0:1 (95% CI: 1.4, 3.0) that they would make a final decision to take LTP-HRT. For each one unit increase in the uncertainty subscale of the decision conflict scale the odds were 0.4:1 (95% CI: 0.2, 0.7) that they would make a final decision to take LTP-HRT or 2.5:1 that they would make a final decision to not take LTP-HRT. Finally, when the physician felt that the patient should be taking LTP-HRT the odds were 78.0:1 (95% CI: 6.2, 975.0) that they would make a final decision to take LTP-HRT.

Table 4.2.3.2. Models for the Decision Two Months after the Counseling Interview (Primary Objective)

Models / Variables	OLR OR(95% CI)	GEE and GEE Reduced OR (95%) CI	GEE Stepwise OR (95% CI)
Intervention	0.53 (0.14, 1.95)	**0.57 (0.14, 2.28)**	0.58 (0.16, 2.04)
Doctor Preference	271.42 (26.82, 999)	**77.99 (6.24, 974.87)**	61.98 (7.09, 541.80)
MENQoL pshychological subscale	2.13 (1.39, 3.59)	**2.01 (1.35, 2.99)**	2.19 (1.49, 3.23)
DCS uncertainty	0.33 (0.14, 0.66)	**0.37 (0.20, 0.69)**	0.31 (0.17, 0.57)
Family History of Heart Disease	4.21 (1.16, 17.27)	**4.01 (1.37, 11.78)**	4.13 (1.25, 13.67)
Family history breast cancer			0.07 (0.00, 2.30)
Model Statistics			
Hosmer and Lemeshow	3.1346 (p=0.9256)	**6.53027 (p=0.59)**	6.35052 (p=0.61)
Shrinkage		**0.86**	0.82
External validation (HL) n=31		**12.4522 (p=0.13)**	30.2137 (p<0.01)

The Final Model is in the Column with Boldface
* The models are defined as:
OLR = The model was developed using Ordinary Logistic Regression
GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations
GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations
GEE Reduced = The GEE Stepwise model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10

4.2.3.3. Model Validation of the Primary Objective

The data was validated using the dataset of 55 patients described in Section 3.3.2. Of the 31 patients considered, 7 patients decided to take LTP-HRT. The HL was 12.452 (p=0.13). The p-value is greater than 0.05 so it is not possible to prove that the model is not predicting the decision. Therefore, there is support that this model is a good fit and predicts the final decision to take LTP-HRT at the follow-up visit two months after the counseling visit.

4.2.4. Predicting the Uncertain Group after the Decision Intervention (Secondary Objective 1b)

4.2.4.1. Univariate Analysis of Secondary Objective 1b

The variables that were significantly related to the group of women who were uncertain regarding their preference to take LTP-HRT after the intervention by the univariate and adjusted univariate analysis are presented in Table 4.2.4.1. Patients with a family history of heart disease or breast cancer were more likely to be certain about their preference. Patients with a higher score on both the physical and mental subscales of the SF-12 (less physical and mental discomfort respectively) were more likely to be certain at the univariate level when adjusted for the physician. Patients with a higher knowledge score and expectations regarding their risk of heart disease, osteoporosis, and breast cancer that were realistic were more likely to be uncertain about their preference towards LTP-HRT when adjusted for physician. Patients who were uncertain placed a higher value on the importance of heart disease and breast cancer but a lower value on the importance of osteoporosis. Regarding the decision conflict scale, the overall scale and all the subscales were higher (more decisional conflict) among patients who were uncertain.

Table 4.2.4.1. Univariate Analysis for Predicting the Uncertain Group after the Decision Intervention (Secondary Objective 1b)

Variable name	No/Yes (n=77)	Uncertain (n=49)	p-value^	p-value‡
Design				
Intervention % DA§	61.0*	55.1	0.509	0.874
Patient Characteristics				
FHx of Heart Disease	36.4	26.5	0.251	0.006
FHx of Breast Cancer	22.1	6.1	0.017	0.021
SF-12 Physical subscale	26.8 (5.9)†	25.5 (5.7)	0.258	0.086
SF-12 Mental subscale	50.8 (7.3)	53.5 (6.2)	0.033	0.005
Perception of the Decision				
Knowledge	77.7 (18.0)	81.4 (14.0)	0.217	0.021
Realistic Expectations	33.1 (20.2)	36.0 (0.440)	0.440	0.030
Value of Heart Disease	7.0 (3.1)	8.6 (2.2)	0.002	0.007
Value of Osteoporosis	8.5 (3.0)	8.1 (2.3)	0.001	0.005
Value of Breast Cancer	8.0 (2.8)	8.8 (2.0)	0.077	0.004
Second set DCS total	2.1 (0.6)	2.7 (0.4)	0.000	0.000
Uncertainty subscale	2.5 (1.0)	3.8 (0.8)	0.000	0.000
Knowledge subscale	2.0 (0.6)	2.3 (0.6)	0.006	0.013
Supported subscale	2.1 (0.6)	2.4 (0.6)	0.003	0.004
Values subscale	2.0 (0.6)	2.4 (0.6)	0.002	0.001
Satisfaction subscale	2.0 (0.7)	2.7 (0.5)	0.000	0.000

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at $p<0.10$ for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.4.2. Model Development of Secondary Objective 1b

The models developed for this objective are outlined in Table 4.2.4.2. The GEE Stepwise model was the best model due to an appropriate number of explanatory variables for positive outcomes and the shrinkage statistic and the HL were within the ranges predetermined to be acceptable. The HL for the GEE stepwise model was 6.527 (p=0.59) and the shrinkage statistic was 0.93. The interpretation of the model parameters is as follows. For each one unit increase on the uncertainty subscale of the DCS (more uncertain), the odds were 2.6:1 (95% CI: 1.5, 2.7) that patients would be uncertain regarding their preference towards LTP-HRT. For each one unit increase on a ten point scale measuring the importance of osteoporosis, the odds were 1.3:1 (95% CI: 1.1, 1.6) that they would be uncertain. For each one unit increase on the decision conflict satisfaction subscale (less satisfied), the odds were 3.4:1 (95% CI: 1.0, 11.6) that they would be uncertain.

Table 4.2.4.2. Models for Predicting the Uncertain Group after the Decision Intervention (Secondary Objective 1b)

Models	OLR	GEE	GEE stepwise
Variables	**OR(95% CI)**	**OR (95%) CI**	**OR (95% CI)**
Intervention	0.76 (0.26, 2.13)	0.76 (0.31, 1.84)	**0.98 (0.35, 2.74)**
DCS uncertainty	2.42 (1.32, 4.72)	2.50 (1.45, 4.31)	**2.60 (1.47, 4.60)**
Value of Osteoporosis	1.34 (1.09, 1.68)	1.34 (1.06, 1.68)	**1.29 (1.07, 1.57)**
DCS Satisfaction subscale	4.61 (1.56, 16.45)	4.46 (1.56, 12.76)	**3.45 (1.03, 11.58)**
Family history breast cancer	0.15 (0.02, 0.74)	0.16 (0.03, 0.88)	
Knowledge	1.03 (1.00, 1.07)	1.03 (1.00, 1.06)	
Model Statistics			
Hosmer and Lemeshow	6.922 (p=0.5451)	7.0438 (p=0.53)	**6.52738 (p=0.59)**
Shrinkage	0.91	0.88	**0.93**
External Validation n=55		8.082 (p=0.42)	**5.40695 (p=0.71)**

The Final Model is in the Column with Boldface
* The models are defined as:
OLR = The model was developed using Ordinary Logistic Regression
GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations
GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations

4.2.4.3. Model validation of Secondary Objective 1b

The data was validated using the dataset of 55 patients described in Section 3.3.2. All 55 patients were included, of which 24 were uncertain and 31 were certain. The HL was 5.407 (p=0.71). The p-value is greater than 0.05 so it is not possible to prove that the model is not predicting the decision. Therefore, there is support that this model is a good fit and predicts the women who are uncertain about their preference to take LTP-HRT after reviewing the decision intervention.

4.2.5. Predicting the Uncertain Group after the Counseling Interview (Secondary Objective 2b)

4.2.5.1. Univariate analysis of Secondary Objective 2b

The variables that were significantly related to the group of women who were uncertain regarding their initial decision to take LTP-HRT after the counseling interview by the univariate and adjusted univariate analysis are presented in Table 4.2.5.1. Women were more likely to be uncertain about their initial decision if their last menstrual period was remote, had a history of diabetes, elevated triglycerides, or a family history of breast cancer. The patients who were uncertain had a lower score on the MENQoL vasomotor subscale, a smaller proportion of the recently graduated physicians, and the patients placed a lower value on the importance of osteoporosis. All subscales of the decision conflict scale were higher for the uncertain group (increased decisional conflict). Patients who were uncertain had lower scores on the satisfaction with decision-making subscale and the satisfaction with the decision process subscale (less satisfied).

Table 4.2.5.1. Univariate Analysis for Predicting the Uncertain group after the Counseling Interview (Secondary Objective 2b)

Variable name	No/Yes (n=91)	Uncertain (n=34)	p-value^	p-value‡
Design				
Intervention§	58.2*	58.8	0.953	0.903
Patient Characteristics				
Last Menstrual Period	8.2 (6.8)†	11.0 (8.2)	0.055	0.072
Diabetes	2.2	8.8	0.093	0.079
High Triglycerides	4.4	11.8	0.134	0.086
FHx of Breast Cancer	19.8	5.9	0.059	0.058
MENQoL Vasomotor subscale	3.0 (2.0)	2.3 (1.8)	0.087	0.082
Physician Characteristics				
Year of Graduation (% >1978)	57.1	35.3	0.030	0.000
Perception of the Decision				
Value of Osteoporosis	6.9 (3.0)	7.8 (2.5)	0.093	0.015
DCS Total	1.9 (0.5)	2.6 (0.4)	0.000	0.000
Uncertainty subscale	2.2 (0.8)	3.5 (0.8)	0.000	0.000
Knowledge subscale	1.8 (0.6)	2.2 (0.5)	0.002	0.001
Supported subscale	1.8 (0.5)	2.4 (0.6)	0.000	0.000
Values subscale	1.9 (0.6)	2.6 (0.4)	0.000	0.000
Satisfaction subscale	1.8 (0.6)	2.6 (0.4)	0.000	0.000
Evaluation of Decision				
Satisfaction with decision	11.9 (1.8)	9.8 (1.7)	0.000	0.000
Satisfaction with process	47.4 (7.7)	45.4 (6.8)	0.199	0.090

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at $p<0.10$ for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.5.2. Model Development of Secondary Objective 2b

The models developed for this objective are outlined in Table 4.2.5.2. The models developed by the GEE and GEE Stepwise included different variables. The sample size for the development of these models was 125, with 45 positive outcome events. The GEE Stepwise model included five variables for only 45 positive outcome events. Therefore, the variable that was least statistically contributing was eliminated to yield a model that will be referred to as GEE Reduced. For the GEE Reduced model the HL was 2.703 (p=0.95) and the shrinkage statistic was 0.90. The interpretation of the model parameters is as follows. For each unit increase in the decision conflict satisfaction subscale (less satisfied), the odds were 9.6:1 (95% CI: 2.9, 32.2) that the patients would be uncertain about their initial decision to take LTP-HRT. For each unit increase in the decision conflict uncertainty subscale (more uncertain), the odds were 3.4:1 (95% CI: 1.7, 7.1) that the women would be uncertain. For women who had a family history of breast cancer the odds were 0.2:1 (95% CI: 0.1, 0.6) that they would be uncertain about their initial decision to take LTP-HRT or 5:1 that they would be certain about their initial decision to take LTP-HRT.

Table 4.2.5.2. Models for Predicting the Uncertain group after the Counseling Interview (Secondary Objective 2b)

Models	OLR	GEE	GEE Stepwise	GEE Reduced
Variables	**OR(95% CI)**	**OR (95%) CI**	**OR (95% CI)**	**OR (95% CI)**
Intervention	0.34 (0.08, 1.22)	0.37 (0.10, 1.37)	0.47 (0.20, 1.11)	**0.48 (0.22, 1.03)**
DCS Satisfaction subscale	23.23 (5.27, 141.33)	22.78 (4.53, 114.47)	10.03 (2.84, 35.42)	**9.63 (2.88, 32.19)**
DCS uncertainty	4.68 (2.05, 12.49)	4.73 (1.94, 11.51)	3.74 (1.65, 8.51)	**3.45 (1.67, 7.09)**
Last menstrual period	1.12 (1.03, 1.22)	1.11 (1.02, 1.21)		
History of Breast Cancer			0.21 (0.07, 0.57)	**0.23 (0.09, 0.60)**
MENQoL Vasomotor subscale			0.75 (0.58, 0.97)	
Model Statistics				
Hosmer and Lemeshow	5.684 (p=0.68)	4.6111 (p=0.80)	4.708 (p=0.79)	**2.703 (p=0.95)**
Shrinkage	0.93	0.88	0.87	**0.90**
External Validation n=55		34.997 (p<0.01)	33.798 (p<0.01)	**40.637 (p<0.01)**

The Final Model is in the Column with Boldface
* The models are defined as:
OLR = The model was developed using Ordinary Logistic Regression
GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations
GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations
GEE Reduced = The GEE Stepwise model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10

4.2.5.3. Model Validation of Secondary Objective 2b

The data was validated using the dataset of 55 patients described in Section 3.3.2. Fifty-five patients were in the validation set, with 11 being uncertain and 44 being certain. The HL was 33.798 (p=<0.01) and 40.637 (p=<0.01) for the GEE Stepwise and GEE Reduced model respectively. Therefore this model was unable to predict whether a woman would be uncertain regarding her initial decision to take LTP-HRT after the counseling interview with the physician.

4.2.5.4. Development of a Model for Secondary Objective 2b using the Complete Dataset

Since the model was not reproducible with the split sample of the dataset, the model development process was implemented and conducted using the entire dataset. Predicting the uncertain group after the physician visit may be more complex than predicting the uncertain group after the decision intervention. All the physician characteristics as well as the perception of the physician of the decision and the perception of the patient of the evaluation of the decision may be contributing to this uncertainty. Given the increased complexity of the decision-making process at this point, due to the physician and the interaction between the patient and the physician, it is likely a successful model will be developed with a larger sample size. Validation of the model developed utilizing the complete dataset can not be done using a split sample technique.

4.2.5.4.1. Univariate Analysis of Secondary Objective 2b using the Complete Dataset

The variables that were significantly related to the group of women who were uncertain regarding their initial decision to take LTP-HRT after the counseling interview by the univariate and adjusted univariate analysis for the complete dataset are presented in Table 4.2.5.4.1. Women were more likely to be uncertain about their initial decision if their last menstrual period was remote, had a history of diabetes, or a family history of breast cancer. All subscales of the decision conflict scale were able to discriminate between the certain and uncertain group. Patients who were uncertain had a lower score on the satisfaction with decision-making subscale and the satisfaction with the decision process subscale.

Table 4.2.5.4.1. Univariate Analysis for Predicting the Uncertain Group after the Counseling Interview Using the Complete dataset (Secondary Objective 2b)

Variable name	No/Yes (n=135)	Uncertain (n=45)	p-value^	p-value‡
Design				
Intervention§	62.2*	62.5	0.576	0.712
Patient Characteristics				
Last Menstrual Period	7.5 (6.4)†	9.5 (8.2)	0.081	0.164
Diabetes	3.7	11.1	0.060	0.090
History of Breast Cancer	16.3	6.7	0.106	0.092
Perception of the Decision				
DCS Total	2.0 (0.5)	2.6 (0.4)	0.000	0.000
Uncertainty subscale	2.3 (0.9)	3.5 (0.7)	0.000	0.000
Knowledge subscale	1.8 (0.5)	2.1 (0.5)	0.001	0.002
Supported subscale	1.9 (0.6)	2.4 (0.5)	0.000	0.000
Values subscale	1.9 (0.5)	2.3 (0.5)	0.000	0.001
Satisfaction subscale	1.9 (0.6)	2.6 (0.4)	0.000	0.000
Evaluation of Decision				
Satisfaction with decision	11.8 (1.8)	9.9 (1.6)	0.000	0.000
Satisfaction with process	47.5 (7.3)	45.0 (6.8)	0.038	0.009

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at p<0.10 for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.5.4.2. Model Development of Secondary Objective 2b using the Complete Dataset

The models developed for this objective are outlined in Table 4.2.5.2.2. Interestingly, the same covariates are included in the two models GEE and GEE Stepwise and in the GEE and GEE Reduced models when only the development set of this dataset was utilized for model development. For both these models the shrinkage statistic, the Hosmer and Lemeshow test statistic, and the number of covariates included in the model met the predetermined criteria.

Table 4.2.5.4.2. Models for Predicting the Uncertain Group after the Counseling Interview Using the Complete Dataset (Secondary Objective 2b)

Models	OLR	GEE	GEE Stepwise
Variables	OR(95% CI)	OR (95%) CI	**OR (95% CI)**
Intervention	1.29 (0.51, 3.32)	1.27 (0.54, 2.99)	**1.19 (0.56, 2.53)**
DCS Satisfaction subscale	16.79 (5.38, 61.05)	16.68 (6.11, 45.49)	**11.04 (3.87, 31.48)**
DCS uncertainty	2.73 (1.47, 5.30)	2.71 (1.38, 5.34)	**2.19 (1.16, 4.10)**
Last menstrual period	1.08 (1.02, 1.16)	1.08 (1.00, 1.16)	
History of Breast Cancer			
MENQoL Vasomotor			**0.35 (0.11, 1.14)**
Model Statistics			
Hosmer and Lemeshow	3.3168 (p=0.9129)	5.73422 (p=0.68)	**7.33354 (p=0.50)**
Shrinkage		0.93	**0.94**

The Final Model is in the Column with Boldface

* The models are defined as:

OLR = The model was developed using Ordinary Logistic Regression

GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations

GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations

GEE Reduced = The GEE Stepwise model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10

The reproducibility of this model was not performed at this time due to a lack of a validation set. Further data will become available as the RCT nears completion and reproducibility will be considered at that time.

4.2.6. Change in Opinion after the Counseling Interview (Secondary Objective 3)

Forty-two women changed their opinion regarding the decision to take LTP-HRT after reviewing the intervention as compared to their decision after the counseling interview. The changes are illustrated in Table 4.2.6. There were changes in all directions, but 25 of the 42 women who were unsure after reviewing the intervention became certain (yes or no) after the counseling interview.

Table 4.2.6. Cross-tabulation of Decision after Reviewing Intervention compared to Decision after Counseling Interview

Decision after Counseling Interview	Decision after Reviewing Intervention				
	No	Unsure	Yes	Total	Changed*
No	41	13	3	57	16
Unsure	8	24	3	35	11
Yes	3	12	19	34	15
Total	52	49	25	126	42

* the number of women whose opinion changed from after reviewing the intervention to after the counseling interview

4.2.6.1. Univariate Analysis of Secondary Objective 3

The variables that were significantly related to the group of women whose opinion to take LTP-HRT changed from the time after they reviewed the decision intervention to after they had their counseling interview by the univariate and adjusted univariate analysis are presented in Table 4.2.6.1. This analysis was performed to identify factors that were modifiable by the influence of the physician. Women who changed their opinion were of younger age, less educated, had a history of hypertension or high cholesterol. Regarding the quality of life measures, women who changed their preference had higher scores (more distress) on all subscales of the MENQoL. For the perception of the decision category, women who had changed their opinion placed a higher value on the importance of heart disease, osteoporosis, and breast cancer. Women were also more likely to change their opinion with less realistic expectations and higher levels of uncertainty as measured by the decision conflict scale. Women were less likely to change their opinion if they had a higher level of satisfaction with their decision and the decision making process.

Table 4.2.6.1. Univariate Analysis for Change in Opinion after the Counseling Interview (Secondary Objective 3)

Variable name	No (n=84)	Yes (n=42)	p-value^	p-value‡
Design				
Intervention§	61.9*	52.4	0.306	0.805
Patient Characteristics				
Age	56.4 (6.0)†	54.0 (6.6)	0.046	0.026
Education (%some postsecondary)	76.2	52.4	0.007	0.004
Last Menstrual Period	9.0 (7.4)	8.7 (7.1)	0.848	0.034
Hypertension	19.0	35.7	0.041	0.009
High Cholesterol	17.9	40.5	0.006	0.009
FHx of Breast Cancer	21.4	4.8	0.016	0.035
MENQoL Vasomotor subscale	2.6 (1.8)	3.1 (2.2)	0.150	0.033
MENQoL Psychosocial subscale	2.8 (1.5)	3.5 (1.6)	0.022	0.004
MENQoL Physical subscale	3.0 (1.3)	3.7 (1.4)	0.008	0.005
MENQoL Sexual subscale	2.3 (1.8)	2.8 (2.1)	0.155	0.028
Physician Characteristics				
CCFP %yes	76.2	61.9	.	0.053
Perception of the Decision				
Realistic Expectations	35.7 (24.2)	25.1 (16.9)	0.012	0.007
Value of Heart Disease	7.0 (3.0)	8.4 (2.2)	0.010	0.008
Value of Osteoporosis	6.8 (3.0)	7.9 (2.5)	0.046	0.019
Value of Breast Cancer	7.8 (2.8)	8.8 (1.8)	0.059	0.015
DCS Total	2.0 (0.6)	2.2 (0.5)	0.092	0.012
Uncertainty subscale	2.4 (1.0)	2.9 (0.8)	0.008	0.000
Satisfaction subscale	2.0 (0.7)	2.2 (0.6)	0.137	0.017
Evaluation of Decision				
Satisfaction with decision	11.5 (2.1)	10.8 (1.8)	0.073	0.020
Satisfaction with process	47.8 (7.5)	44.7 (7.3)	0.030	0.022

p-value^ refers to the univariate analysis not accounting for the physician cluster
p-value‡ refers to the univariate analysis accounting for the physician cluster adjusted for correlation
§ The intervention and all variables that are significant at p<0.10 for the univariate or adjusted univariate analysis
* categorical variables are presented as percentages
† continuous variables are presented as means and standard deviations

4.2.6.2. Model Development of Secondary Objective 3

The models developed for this objective are outlined in Table 4.2.6.2. The GEE and GEE Stepwise models were the same. Reduced models were fit to maximize the shrinkage statistic, to have a non-significant HL, and no more than 10 outcome events for each covariate included in the model. The best GEE Reduced model as defined by the above criteria, included the following variables: intervention, the uncertainty subscale of the DCS, education, the psychological subscale of the MENQoL, and a history of hypertension (last column of table 4.2.6.2.). This model had a HL of 12.875 (p=0.12) and a shrinkage statistic of 0.92. The interpretation of the model parameters is as follows. For patients randomized to the decision aid, the odds were 0.4:1 (95% CI: 0.2, 0.8) that they would change their mind after the physician visit compared to the patients randomized to the pamphlet or were 2:1 that they would not change their mind. This was the only one of all the models where the decision intervention was found to significantly contribute to the model. For patients with more education the odds were 0.2:1 (95% CI: 0.1, 0.5) that they would change their opinion or 5:1 that they would not. For each unit increase in the uncertainty subscale of the decision conflict scale (more uncertain), the odds were 2.0:1 (95% CI 1.3, 2.8) that they would change their opinion. For each unit increase in the psychological subscale of the MENQoL (more psychological distress), the odds were 1.4:1 (1.1, 1.6) of changing their opinion. If the patient had a history of hypertension the odds were 2.7:1 (95% CI 1.1, 6.7) that they would change their opinion.

Table 4.2.6.2. Models for Change in Opinion after the Counseling Interview (Secondary Objective 3)

Models	OLR	GEE & GEE Stepwise	GEE Recduced
Variables	**OR(95% CI)**	**OR (95%) CI**	**OR (95% CI)**
Intervention	0.4 (0.1, 1.1)	0.4 (0.2, 0.9)	**0.4 (0.2, 0.8)**
Uncertainty subscale DCS	2.2 (1.3, 3.7)	2.2 (1.4, 3.4)	**1.9 (1.3, 2.8)**
Education some postsecondary	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	**0.2 (0.1, 0.5)**
MENQoL psychological subscale	1.4 (1.0, 1.9)	1.4 (1.1, 1.7)	**1.4 (1.1, 1.6)**
Hypertension	3.7 (1.3, 11.2)	3.7 (1.3, 10.4)	**2.7 (1.1, 6.7)**
CCFP (0/1)	0.2 (1.3, 3.7)	4.0 (1.6, 9.8)	
High Cholesterol	3.7 (1.4, 10.6)	3.7 (1.4, 9.7)	
Age	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	
Model Statistics			
Hosmer and Lemeshow	14.691 (p=0.06)	16.321 (p=0.04)	**12.875 (p=0.12)**
Shrinkage		0.86	**0.92**
External validation n=55		28.699 (p<0.01)	**22.217 (p<0.01)**

The Final Model is in the Column with Boldface

* The models are defined as:

OLR = The model was developed using Ordinary Logistic Regression

GEE = The model was developed using the variables from OLR model and using Generalized Estimating Equations

GEE Stepwise = The model was developed using a stepwise algorithm with Generalized Estimating Equations

GEE Reduced = The GEE Stepwise model was reduced by deleting the least significant covariate until the shrinkage coefficient was > 0.85, the Hosmer-Lemeshow statistic was non-significant, and the number of covariates was approximately equal to the number of positive outcome events divided by 10

4.2.6.3. Model Validation of Secondary Objective 3

The model was applied to a dataset of the next consecutive 55 patients enrolled in the trial. Of these patients in this validation set, 26 patients changed their opinion and 29 patients did not. The HL was 22.217 ($p<0.01$). Therefore this model was unable to predict whether a woman would change her opinion regarding the use of LTP-HRT before and after the counseling interview.

The model was not redeveloped utilizing the complete dataset as it was felt that useful information was not added when this was done for Secondary Objective 2b.

4.3 Summary of Results

The 6 models that were developed from the development dataset of 126 patients are summarized in Table 4.3. Four of the 6 models were reproducible using the next 55 patients enrolled in the RCT. The two models that were not reproducible were predicting the change in opinion regarding LTP-HRT from after reviewing the intervention to after the counseling visit with the physician (Objective S3) and predicting the uncertain group after the counseling visit with the physician (Objective S2b).

Table 4.3. Summary of all Models

Models (yes vs no)	Secondary Obj 1a*	Secondary Obj 2a*	Primary Objective*
Design			
Intervention	0.91 (0.25, 3.28)	0.30 (0.09, 0.98)	0.58 (0.15, 2.24)
Patient Characteristics			
Hysterectomy	11.63 (3.92, 34.50)		
FHx of Heart Disease			3.99 (1.36, 11.72)
MENQoL Phys subscale		2.30 (1.34, 3.95)	
MENQoL Vaso subscale		1.37 (1.10, 1.70)	
MENQoL Psycho. subscale			1.99 (1.34, 2.96)
Perception of the decision			
S2 Value of Heart Disease	2.519 (1.572, 4.036)		
S2 Value of Breast Cancer	0.489 (0.348, 0.688)		
S3 DCS Uncertainty subscale			0.378 (0.206, 0.697)
Perception of the physician			
Physician prescribe HRT		62.03 (13.28, 289.66)	77.94 (6.24, 973.60)
Models (uncertainty)	**Secondary Obj 1b***	**Secondary Obj 2b**	**Secondary Obj 3**
Design			
Intervention	0.98 (0.35, 2.74)	0.34 (0.108, 1.072)	0.38 (0.18, 0.84)
Patient Characteristics			
Education			0.23 (0.10, 0.54)
Last Menstrual Period		1.11 (1.03, 1.20)	
High Blood Pressure			2.68 (1.08, 6.67)
Perception of the decision			
S2 Value of Osteoporosis	1.29 (1.07, 1.57)		
S2 DCS Uncertainty subscale	2.60 (1.47, 4.60)		
S2 DCS satisfaction subscale	3.45 (1.03, 11.58)		
S3 DCS Uncertainty subscale		5.95 (2.42, 14.62)	1.94 (1.34, 2.83)
S3 DCS Satisfaction subscale		23.32 (5.36, 101.46)	

* model reproducible

The three important time points when a preference, an initial decision, and a final decision regarding LTP-HRT were measured were after the intervention (T1), after the physician visit (T2), and at the 2-month follow-up visit (T3), respectively. After reviewing the intervention, the variables that were important in predicting a woman's preference regarding LTP-HRT (Secondary Objective 1a) were whether or not she had a hysterectomy, placement of high value on the importance of heart disease and placement of a low value on the importance of breast cancer. After the counseling interview with the physician, the variables that were predictive of the initial decision to take LTP-HRT (Secondary Objective 2a) were a high score on the MENQoL physical and vasomotor subscales and if the physician would prescribe LTP-HRT if the decision was up the physician alone. At the two-month follow-up visit, the variables that were predictive of the final decision to take LTP-HRT (Primary Objective) were a family history of heart disease, a higher score on the psychological subscale of the MENQoL, a low score on the decision conflict uncertainty subscale and if the physician would prescribe LTP-HRT if the decision was up the physician alone.

To identify the uncertain group after reviewing the intervention (Objective S1b), the variables that were predictive women were placing a higher value on the importance of osteoporosis and higher scores on the uncertainty (more uncertain) and the satisfaction (less satisfied) subscales of the decision conflict scale.

5. Discussion

5.1. Interpretation of the Results of the Decision to take LTP-HRT

LTP-HRT use was considered at three time points in this study, within 24 hours of the decision intervention being reviewed (Secondary Objective 1a), within 24 of the counseling interview with the physician (Secondary Objective 2a), and two months after the counseling interview. At each time point the number of women who were uncertain diminished (Figure 2). There was some variation in the factors that were associated with the decision at each of these three time points. This variation has a number of possible explanations. First, the number of women who had made a decision at each time point increased. Second, the number of women analyzed at each time point was small and therefore the number of factors that were included in each model limited. Last, there may be a shift over time in the factors that are important in the decision to take LTP-HRT.

5.1.1. Preference after the Decision Intervention (Secondary Objective 1a)

The factors that were associated with a preference to consider taking LTP-HRT after reviewing a decision support intervention were hysterectomy status, the importance placed on the value of heart disease and breast cancer (a high value for heart disease and a low value for breast cancer).

The odds ratio of 12:1 for women with a hysterectomy was the strongest factor influencing the preference to take LTP-HRT. Hysterectomy status has been confirmed in other studies as an important factor associated with the use of HRT[49-51; 54-57; 59-62; 64-66; 68; 69; 71; 79; 80; 98]. This is clinically justified. The ACP guidelines recommends that women who have had a hysterectomy should consider LTP-HRT[7]. Also, many women who have had a hysterectomy may perceive themselves to have a deficient hormonal state and thus be more inclined to consider LTP-HRT.

O'Connor et al. have been the only ones to describe the relationship between values and LTP-HRT choice following a decision intervention[4]. In a study to assess the acceptability of Decision Aids, a cohort of 94 women used a decision aid to make a hypothetical decision to take LTP-HRT. Using discriminant function analysis they showed that the values women placed on the benefits and risks of HRT were 84% accurate in discriminating between choices. Those choosing LTP-HRT placed a higher value on the importance of heart disease and a lower value on the importance of breast cancer.

Walsh et al.[72] examined the role that the value that women place on heart disease and breast cancer play as predictors of the decision to take HRT using a questionnaire. The hormone use of each women was classified as either having never used HRT or having used HRT at any time, that is current use or previous use. Women were questioned as to whether or not they were concerned about the development of osteoporosis, heart disease, breast cancer, or uterine cancer. In a multivariate model developed with 126 women, no association was found between importance of benefits and risks and having ever used HRT. This study did not look at these factors when the decision was actually being made. Our study evaluated these factors at the time that the decision was being considered but before the counseling interview with the physician. Therefore, the value that a women places on the risks and benefits of LTP-HRT is important in the decision-making process. Eliciting an explicit value may help women in clarifying their values and lead them to make a better decision for themselves, a decision that they are more comfortable with, and a decision that is durable.

5.1.2. Decision after the Counseling Interview (Secondary Objective 2a)

The factors that were associated with the decision to take LTP-HRT after the counseling interview were physician preference and the physical and vasomotor subscales of the MENQoL (a higher score for both).

The odds ratio of 62:1 for women whose physician preferred LTP-HRT for the woman was the strongest factor influencing the initial decision to take LTP-HRT. There are several hypotheses why this factor may be influential. HRT is a medication that requires a prescription and the physician will be more likely to write a prescription for LTP-HRT when in agreement for its use. The physician may be confirming the patient's preference to take LTP-HRT. Indeed, many of the women started the visit with a strong predisposition toward LTP-HRT. For others, especially those arriving at the visit in a state of uncertainty the physician may guide the patient towards LTP-HRT if they were convinced it was important for their patient or they themselves had a strong preference for its use.

For the studies that considered inputs into decision-making about HRT, 5 studies addressed the advice of the physician. Four of these 5 studies reported a positive correlation between the advice of the physician and the decision to take LTP-HRT. Kadri found that women were more likely to take or had taken LTP-HRT if they had felt that the doctor was an important source of information[79]. Ferguson et al.[78] compared women who were currently taking HRT with women who had never taken HRT. Women were asked to rank the strength of opinion of their physician regarding their use of HRT. Women currently taking HRT rated the recommendation of the physician more positively then those who had never taken it before. Leveille et al.[55] examined the extent that the physician encouraged the use of HRT. This study evaluated a much older population (age 65 to 80 years of age) compared to our study. They found using multivariate analysis that older women were three times more likely to initiate LTP-HRT if they received positive encouragement from their physician. The study by Walsh et al. was a cross-sectional survey of 126 women[72]. Physician recommendation was strongly associated with having ever used HRT as compared to having never used HRT with an odds ratio of 22.8:1. The study by Blumberg found that a higher percentage of women taking HRT had discussed it with their physician than those not taking HRT[73].

These four studies support that the advice of the physician is an important factor in identifying women who are or were taking HRT. In our study, we showed that the preference of the physician for the woman to take LTP-HRT was correlated with the actual decision to take LTP-HRT. This could be due to positive encouragement by the physician, a strong recommendation and guidance towards the decision, or the physician taking control of the decision. The patient-physician relationship and the decision-making process between the women and her physician would need to be evaluated in more detail to understand the complexities of the interaction between the patient and the physician. The amount of negotiation and patient-centered discussion during the office visit and its effect on the decision could also be examined. We do know that the majority of women entering into the RCT desired a process of shared decision-making and when questioned after the counseling interview these women had felt that this process had occurred. Therefore, it is likely that the physician is encouraging the patient or affirming their decision.

This study demonstrates that the MENQoL is an important tool for identifying women who are considering LTP-HRT. The MENQoL has not been studied as a factor influencing the decision to take LTP-HRT before. It is understandable from a clinical viewpoint that if a woman is having symptoms that are related to menopause issues she would be more likely to consider LTP-HRT. The MENQoL was correlated at the univariate level in the previous analysis (after reviewing the decision intervention) and at this time point (after the counseling interview) the physical and vasomotor subscales of the MENQoL are correlated with the decision to take at the multivariate level. The physician may have reviewed the benefits of LTP-HRT for women who are symptomatic and certainly it is reasonable to try a treatment if one is having symptoms. Future research using the MENQoL is warranted. The MENQoL could be used as a screening instrument to identify women who having symptoms related to menopause and should have further discussions regarding the use of LTP-HRT.

5.1.3. Decision Two Months after the Counseling Interview (Primary Objective)

The factors that were associated with the decision to take LTP-HRT two months after the counseling interview were the physician preference for LTP-HRT, a high score on the psychological subscale of the MENQoL, high uncertainty on the uncertainty subscale of the DCS, and a family history of heart disease.

The odds ratio of 78:1 in women whose physician preferred LTP-HRT continued to be the strongest factor influencing the decision to take LTP-HRT two months after the counseling interview. The decision to take LTP-HRT and remain on this treatment is not one that is taken lightly by post-menopausal women. The physician preference is a strong predictor for this reason. Women need affirmation that they are making the right decision for themselves. Therefore when the physician is advocating LTP-HRT, women are more likely to take it.

A family history of heart disease was the next strongest factor influencing the decision to take LTP-HRT. This study was designed and implemented before the results of the HERS study was published[5]. Thus the benefit of LTP-HRT in the prevention of CHD quoted in the pamphlet and decision aid was a reduction of 30 to 50%. This may still be a reliable risk reduction quote for women who do not have pre-existing coronary heart disease but the HERS statement has raised uncertainty about the reliability. Therefore, if the RCT was started today, this covariate may not have been included in the model. Heart disease was assessed in a number of ways: first, whether or not the patient had heart disease; second, whether or not she had a family history of early heart disease (CHD in a first-degree relative less than 55 years if a male and less than 65 years if a female); and last, by the importance that she placed on heart disease on a scale of 1 to 10. In the RCT, very few women had heart disease or reported having heart disease (4.8% of the study population). Both the importance a woman placed on the value of heart disease and having a family history of heart disease was significant in the univariate analysis. These two variables were not correlated with each other in our cohort; the Pearson correlation coefficient was 0.11. Family history is the more objective covariate; that is, it can be reliably ascertained in each woman. The more objective covariate may have been included, as the physician preference was such a strong predictor in the actual decision to take LTP-HRT. For example, if the physician knows a woman has a positive family history of heart disease then they may be more likely to encourage the use or make their opinion strongly heard.

In our review there were 5 studies that had addressed family history of early heart disease as a determinant of the decision to take HRT[71; 72; 74; 99; 100]. Two of the studies were cross-sectional in design and employed a multivariate analysis. The study by Walsh et al had a sample size of 126[72] and the study by Egeland had a sample size of 2,137[71]. Two studies were prospective cohort studies that only employed a univariate analysis[99; 100] and the last study was a case-control study that again only employed a univariate analysis[74].

Women, who chose to take LTP-HRT were also less uncertain, that is they had a lower decisional conflict on the uncertainty subscale of the decision conflict scale than those who did not choose LTP-HRT. Making a decision to start a new treatment requires an action; deciding not to take LTP-HRT may be an action but also may be a passive response. One usually does not exist in a perpetual state of uncertainty. The higher uncertainty in the 'no' group could be due to the fact that the decision to not take LTP-HRT was a default decision or due to the fact that the patient was going against their physician's preference. The lower uncertainty in the 'yes' group is reassuring. Women who have decided to take LTP-HRT are comfortable with their decision and may therefore be more likely to stick with their decision. The uncertainty subscale could be used to identify women who require further information or counseling, more support in the decision-making process. More research is required to examine the decision to take LTP-HRT and a low uncertainty score on the uncertainty subscale of the DCS is predictive of continued use of LTP-HRT

Women who chose to take LTP-HRT also had a higher score on the psychological subscale of the MENQoL (more psychological symptoms). It makes sense clinically that if women are distressed regarding the menopause that they would be more likely to consider taking HRT. In the previous analysis, after the counseling interview, the physical and vasomotor subscales were associated with the decision to start taking LTP-HRT. Physical symptoms may be the driving force in a women's decision to start taking LTP-HRT and the psychological symptoms may be the driving force to continue taking LTP-HRT. The MENQoL has not been studied in the context of decision-making regarding the use of HRT before. Further study is needed to confirm that this scale may be an important tool in identifying women who are symptomatic and may consider taking LTP-HRT and continuing to take LTP-HRT for a prolonged period of time.

Hysterectomy status was not significant in the final model. In the development dataset 27.8% of the women had had a hysterectomy. It was significant in the univariate analysis with 51.7% of the women whose final decision was to take LTP-HRT having had a hysterectomy and only 20.2% of the women who did not decide to take LTP-HRT had a hysterectomy. There have been numerous published studies that have supported this covariate as a strong predictor of HRT use[49-51; 54-57; 59-62; 64-66; 68; 69; 71; 79; 80; 98]. The explanation for hysterectomy not being included in the final model was possibly related to the sample size of the study. We did not have sufficient sample size to detect this covariate and the other covariates such as physician preference were stronger predictors.

5.2. Interpretation of the Results to Predict the Uncertain Group

Identification of women who are uncertain at varying stages of the decision-making process is extremely important. These women require more support from the physician to help them to arrive at a decision that is right for them. More support could be provided in many forms, for example, additional information sessions or information given to the patient, more time spent one-on-one with the physician or another health care professional, or assistance in weighing the benefits and risks. The Decision Conflict scale, as has been shown previously[4] is a reliable and reproducible tool for identifying women who are uncertain. This tool would be a useful screening instrument to identify women in clinical practice that will require more time and resources in reaching a decision.

5.2.1. Predicting the Uncertain Group after the Decision Intervention (Secondary Objective 1b)

The factors that were associated with being uncertain regarding the preference to take LTP-HRT after reviewing the decision support intervention were the uncertainty and satisfaction subscales of the DC and the importance that a woman placed on the osteoporosis.

The odds ratio of 3.5:1 for each one unit increase in the score of the DCS satisfaction subscale was the strongest factor identifying the uncertain group after the decision intervention. A higher score on this subscale implies that the woman is less satisfied with the decision and the decision-making process. The Decision Conflict Scale is a validated scale that has satisfactory reliability and discriminates between those who make and delay decisions[101]. There have been no previous studies that have evaluated decisional conflict as a factor influencing the preference to take LTP-HRT. O'Connor et al. have shown in a previous study that decisional conflict was higher before reviewing a decision aid than afterwards[4]. The satisfaction and uncertainty subscales appear to be important in identifying women who are uncertain. Having a reliable instrument to identify those women who are uncertain could be important in clinical practice as this may be a group that requires more targeted interventions and more time spent counseling regarding options. The other dimensions of the scale provide information on the factors contributing to uncertainty to direct counseling and interventions.

The importance placed on the value of osteoporosis was a significant factor in identifying those women who were uncertain after reviewing the decision support intervention. This may be related to the fact that there are many options to be considered for the treatment and prevention of osteoporosis[3]. This variable was not important in subsequent models later in the decision-making process. This may be due to the fact that the physician at the counseling interview clarified the options for osteoporosis.

5.2.2. Predicting the Uncertain Group after the Counseling Interview (Secondary Objective 2b)

A model was developed for this objective but it did not validate in the split sample of the database. The complete database of 180 patients was used to redevelop the model. Using the same method for determining the factors identifying those who were uncertain after the counseling interview, interestingly, the same variables were included in both models, (i.e., for the smaller and larger data sets). We were unable to validate the model developed on the entire data set. The covariates that were predictive were the satisfaction and uncertainty subscale of the decision conflict scale and the history of breast cancer.

The physician visit is a complex interaction and many different factors may be at play. The uncertain group may have many different attributes and thus make it difficult to predict. When the model was developed on the smaller data set there may have been significant differences between this group and the validation data set. When all were included in the model development the same three predictors were still the strongest predictors but they may have not been as strong. At this time we were not able to validate the model developed on the entire dataset.

5.2.3. Change in Opinion after the Counseling Interview (Secondary Objective 3)

This model also did not validate using the validation subset. Due to software limitations at this time we were unable to implement and conduct the model development in the entire dataset.

This model was originally proposed to try and explore the physician-patient relationship more closely. When we evaluated the shift in opinion more closely we realized we were not dealing with one group that would be easy to predict. There were 42 women who changed their opinion. All six possible combinations of change occurred between 'yes', 'no', and 'unsure'. Thus, different factors may be associated with the change in opinion depending on the direction of the change. The physician patient interaction is extremely complex, these shifts indicate that the physician may have considerable influence over the women's decision. It would be interesting to examine these shifts individually but a larger sample size would be required.

5.3. Limitations

5.3.1. Models

The models were developed using multivariate modeling techniques. Due to the fact that the physician was the unit of randomization, a technique had to be used that allowed for the analysis of correlated data. Donner et al. has clearly demonstrated that clustering cannot be ignored in the analysis[102] and recommended that any study that randomly assigns intact clusters to treatment groups must inherently assume the existence of intracluster correlation.

Incorporating clusters into the development of predictive models has not been well described. Thus, we attempted two different methods of developing the models: first, using OLR to identify the predictive covariates and then using the GEE method with those covariate to get reliable estimates of the covariates and their standard errors (referred to as the GEE method); second, was to use a stepwise method (referred to as GEE Stepwise), analogous to that used for OLR and described in the methods section. In the four objectives that had models developed and validated in the second subset of the data (secondary objective 1a, 2a, 1b, and the primary objective), three of the objectives had different covariates in the models depending on whether the GEE or GEE Stepwise method were used to develop the models. For secondary objective 2a the variables included in the two methods were different (Table 4.2.2.2.). For the primary objective, the GEE Stepwise included one more variable than the GEE method and when reduced to prevent overdispersion the GEE Reduced model was the same as the GEE model (Table 4.2.3.2.). For secondary objective 1b, the GEE Stepwise included two fewer variables than the GEE model. In each of these objectives the GEE Stepwise or GEE Reduced model was reproducible.

Multivariate analysis allows the evaluation of the important independent variables to confirm that the independent variables retain their importance in the context of the other variables[96]. When individual variables are examined to determine their magnitude of risk, the estimates will vary with the structure of the mathematical model and the coding of the variables. The assumptions and limitations of the multivariate methods become especially important for ensuring accurate results and valid interpretations. The article by Concato et al. gives an excellent overview of the problems with multivariable modeling, which they identify as the following: overfitting, interactions, unspecified coding of variables, unspecified selection of variables, collinearity, validation, identification of statistical package used, and how to correct them[96]. Each of these issues were addressed in the methods section.

A major problem that was faced in the development of the models was the small sample size. Thus overfitting was of particular concern. The recommendations of Harrell et al. for the development of a model[97] were followed as outlined in our methods section. If a model is badly overfitted, the model may actually have negative (worse than random) discrimination on new data, and it will have poor calibration. I do not believe that this was the reason for one of the two models (secondary objective 2b) not being reproducible. For secondary objective 2b when the model development was repeated using the complete dataset the same variables were included in the model. This may be the reason that secondary objective 3 was not reproducible though.

5.3.2. Sampling

The models developed are exploratory or hypothesis generating in nature. It would be difficult in a clinical setting to obtain much of the data that was collected. The data from the randomized controlled trial may not be generalizable for a number of reasons. First, there was a preferential dropout rate between the two groups from the original study. There were more physicians who dropped out from the trial or did not enroll their full complement of patients from the pamphlet group. Use of the pamphlet was probably very similar to usual care, whereas physicians randomized to the decision aid may have been more interested and involved and therefore more willing to continue participation.
Our patient population was predominantly Caucasian, married, and well educated; this may limit the generalizability of the results. Due to the complexity of the physician-patient interaction and the small sample size we were unable to externally validate the two models that looked at the outcome following the physician visit.

6. Future Directions

Research on decision-making is in its infancy. This is the first study that has tried to identify the factors associated with the decision to take LTP-HRT in the context of the Decision Support Framework. I believe that the Decision Support Framework is a construct that is useful in clinical situations that have decisions that are value-laden. The identification of the preference of the physician as a strong factor associated with the decision to take LTP-HRT is an important finding. This highlights the necessity of the physician in discussing the use of LTP-HRT with their patients. If health care professionals, government, and the public feel that shared decision-making is important, we may need to also re-educate the physicians on how to be involved and involve the patient in this process. Identifying the MENQoL as a factor associated with the use of LTP-HRT is also important as this may be a way of identifying women who would benefit from the use of LTP-HRT and should have a physician discuss the use of LTP-HRT with them.

During the decision-making process for the use of LTP-HRT many women were uncertain. The number of women who were uncertain decreased at each time point throughout this process. The DCS, especially the uncertainty and satisfaction subscales, was able to identify women who are uncertain with regards to the use of LTP-HRT. The identification of those women who are uncertain is important since they may require more support, additional follow-up, and more intensive counseling to allow them to make a decision that they are satisfied with. In the primary care setting, to achieve quality decision-making for the use of LTP-HRT more resources and time from health care professionals may be required.

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Ref Type: Report

Appendix 1:

Database: Medline <1966 to February 1999 Week 4>

Search Strategy:

1	exp estrogens/	75300
2	exp estrogens, synthetic/	14605
3	exp hormone replacement therapy/	4503
4	Menopause/ or Postmenopause/	16224
5	exp epidemiologic methods/	1197262
6	educat$.mp.	192854
7	Social class/ or Socioeconomic factors/	43608
8	Employment/ or Unemployment/ or Workplace/	14494
9	Occupations/	10008
10	exp reproductive history/	11418
11	exp Hysterectomy/	12073
12	hysterect$.mp.	15798
13	Smoking/	49439
14	smok$.mp.	73091
15	Health/	6293
16	Health status/	11853
17	Knowledge, attitudes, practice/	10076
18	"KNOWLEDGE".mp.	79961
19	Social values/	5192
20	value$.mp.	459141
21	Health education/ or Patient education/	49041
22	advice.mp.	7648
23	exp attitude of health personnel/ or Physician's role/	37687
24	Physician-patient relations/ or Professional-patient relations/	32670
25	exp Decision making/	25142
26	exp decision support techniques/	15109
27	Patient satisfaction/	7875
28	decision.mp.	28645
29	satisf$.mp.	61976
30	estrogen$.mp.	62247
31	menopaus$.mp.	19951
32	postmenopaus$.mp.	12058
33	perimenopaus$.mp.	864
34	(dat$ adj last adj menstrua$).mp.	49
35	(1 or 2 or 3 or 30) and (4 or 31 or 32 or 33) and ((or/6-29) or 34)	2831
36	5 and 35	1369
37	limit 36 to (human and english language and female)	1263
38	limit 37 to review articles	157
39	37 not 38	1106

Appendix 2: Data Collection Tools

A. Knowledge: We would like to know how familiar you are with hormone therapy before you use the decision support strategy.

Hormone therapy can be given:

Early in menopause	**True**	False	Unsure
Well past the menopause	**True**	False	Unsure
For 10 – 20 years	**True**	False	Unsure

Benefits of taking long-term hormone therapy are:

Protection from breast cancer	True	**False**	Unsure
Protection from broken hips from osteoporosis	**True**	False	Unsure
Protection from diabetes	True	**False**	Unsure
Protection from heart disease	**True**	False	Unsure

Risks of using hormone therapy are:

Increases risk of breast cancer	**True**	False	Unsure
Increases risk of broken bones from osteoporosis	True	**False**	Unsure
Increases risk of diabetes	True	**False**	Unsure
Increases risk of heart disease	True	**False**	Unsure

Some side effects of hormone therapy are:

Breast tenderness	**True**	False	Unsure
Fainting	True	**False**	Unsure
Irritability	**True**	False	Unsure
Bloating	**True**	False	Unsure
Hot Flushes	True	**False**	Unsure
Headache	**True**	False	Unsure
Menstrual Bleeding	**True**	False	Unsure
Insomnia	True	**False**	Unsure
Weight Gain	**True**	False	Unsure

Calculation of the Knowledge score:

Knowledge was calculated by summing the correct answers (in bold) and dividing by the number of questions.

B. Realistic Expectations:

Now are we interested in your opinion about your chances of disease in your lifetime ***without*** hormone therapy.

1. Heart disease - Do you consider yourself to be:

Low risk ___ Average risk______ High risk_____

Out of 100 women like you, how many will have heart disease some time in their life?

All		100 out of 100 women will have heart disease sometime in their life
Most		76 – 99 women out of 100 will have heart disease
The Majority		51 - 75 women out of 100 will have heart disease
Many		26 – 50 women out of 100 will have heart disease
Several		11 – 25 women out of 100 will have heart disease
Some		1 – 10 women out of 100 will have heart disease
None		0 women out of 100 will have heart disease

2. Broken Hips from Osteoporosis - Do you consider yourself to be:

Low risk_____ Average risk ______ High risk ______

Out of 100 women like you, how many will have broken hips from osteoporosis some time in their life?

All		100 out of 100 women will have broken hips some time in their life
Most		76 – 99 women out of 100 will have broken hips
The Majority		51 – 75 women out of 100 will have broken hips
Many		26 – 50 women out of 100 will have broken hips
Several		11 – 25 women out of 100 will have broken hips
Some		1 – 10 women out of 100 will have broken hips
None		0 women out of 100 will have broken hips

3. Breast Cancer - Do you consider yourself to be?

Low risk ______ Average risk _______ High risk _______

Out of 100 women like you, how many will have breast cancer some time in their life?

All		100 out of 100 women will have breast cancer some time in their life
Most		76 – 99 women out of 100 women will have breast cancer
The Majority		51 – 75 women out of 100 women will have breast cancer
Many		26 – 50 women out of 100 women will have breast cancer
Several		11 – 25 women out of 100 women will have breast cancer
Some		1 – 10 women out of 100 women will have breast cancer
None		0 women out of 100 will have breast cancer

Now are we interested in your opinion about your chances of disease in your lifetime ***with*** hormone therapy.

1. Heart Disease

If 100 women like you were to take hormone therapy, how many would be protected from heart disease because they took hormones?

All		100 out of 100 women will be protected because they took hormones
Most		76 – 99 women out of 100 will be protected from heart disease
The Majority		51 – 75 women out of 100 will be protected from heart disease
Many		26 – 50 women out of 100 will be protected from heart disease
Several		16 – 25 women out of 100 will be protected from heart disease
Some		6 – 15 women out of 100 will be protected from heart disease
A Few		1 – 5 women out of 100 will be protected from heart disease
None		0 women out of 100 will be protected from heart disease

2. Broken Hips from Osteoporosis

If 100 women like you were to take hormone therapy, how many would be protected from broken hips from osteoporosis because they took hormones?

All		100 out of 100 women will be protected from broken hips because they took hormones
Most		76 – 99 women out of 100 women will be protected
The Majority		51 – 75 women out of 100 women will be protected
Many		26 – 50 women out of 100 women will be protected
Several		16 – 25 women out of 100 women will be protected
Some		6 – 15 women out of 100 women will be protected
A Few		1 – 5 women out of 100 women will be protected
None		0 women out of 100 women will be protected

3. Breast Cancer

If 100 women like me were to take hormone therapy, how many would get breast cancer because they took hormones?

All		100 out of 100 women will get breast cancer because they took hormones.
Most		76 – 99 women out of 100 will get breast cancer
The Majority		51 – 75 women out of 100 will get breast cancer
Many		26 – 50 women out of 100 will get breast cancer
Several		16 – 25 women out of 100 will get breast cancer
Some		6 – 15 women out of 100 will get breast cancer
A Few		1 – 5 women out of 100 will get breast cancer
None		0 women out of 100 will get breast cancer

Realistic Expectations:

This scale was calculated out of 6. A woman obtained a point if her expectations were realistic for each disease (heart disease, osteoporosis, and breast cancer) with and without HRT. The correct answer for each of the 6 sections was based on the women's medical history.

For example if a woman had a low bone density test. The correct answer for risk of osteoporosis and no HRT would be many women (26-50 women out of 100 will be protected from osteoporosis). The correct answer for risk of osteoporosis with HRT would be some women (6 – 15 women out of 100 women will be protected from osteoporosis)

B. Values

Below are listed some things women consider when making a decision about hormone therapy.

1. How important is protection from heart disease to you when making a decision about hormone therapy?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										Extremely important to me

2. How important is protection from broken hips form osteoporosis to you when making a decision about hormone therapy?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										Extremely important to me

3. How important are the side effects of therapy to you when making a decision about hormone therapy?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										Extremely important to me

4. How important is the risk of breast cancer to you when making a decision about hormone therapy?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										Extremely important to me

Values were considered as a continuous variable from 0 to 10.

B. Decision Conflict Scale

Now thinking about the choice you just made, please look at the following comments made by some women when deciding about hormone therapy.

	1	2	3	4	5
	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
1. This decision is easy for me to make					
2. I'm sure what to do in this decision					
3. It's clear what choice is best for me					
4. I'm aware of the choices I have to reduce by risk of heart disease & osteoporosis					
5. I feel I know the benefits of hormone therapy					
6. I feel I know the risks and side effects of hormone therapy					
7. I have enough advice and information about the choices					
8. I know how important the benefits are to me in this decision					
9. I know how important the risks and side effects are to me in this decision					
10. I know which is more important to me (the benefits or the risks)					
11. I am making this choice without any pressure from others					
12. I have the right amount of support from others in making this choice					
13. I feel I have made an informed choice					
14. My decision shows what is important to me					
15. I expect to stick with my decision					
16. I am satisfied with my decision					

The DCS is calculated by adding the responses to questions 1-16 and dividing by 16.
The uncertainty subscale is calculated by adding the responses to questions 1-3 and dividing by 3.
The knowledge subscale is calculated by adding questions 4-6 and dividing by 3.
The supported subscale is calculated by adding questions 7,11, and 12 and dividing by 3.
The values subscale is calculated by adding questions 8-10 and dividing by 3.
The satisfaction subscale is calculated by adding questions 13-16 and dividing by 4.

I. SF-12th Health Survey

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. In general, would you say your health is:

Excellent ___ Very Good ___ Good ___ Fair ___ Poor _____

2. The following are activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.

Yes, limited a lot ____ Yes, limited a little ____ No, not limited at all ____

b) Climbing several flights of stairs

Yes, limited a lot _____ Yes, limited a little ____ No, not limited at all _____

1. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a) accomplished less than you would like yes_____ no _______

b) were limited in the kind of work or other activities yes _____ no ____

2. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)

a) accomplished less than you would like yes _____ no _____

b) didn't do work or other activities as carefully as usual yes _____ no _____

a) during the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all ___ a little bit ___ Moderately ___ Quite a bit ___ Extremely ____

1. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

	All of the time	Most of the time	A Good bit of the time	Some of the time	A little of the time	None of the Time
Have you felt calm and peaceful?						
Did you have a lot of energy?						
Have you felt downhearted and blue?						

1. During the past 4 weeks, how much of the time have your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc?)

All of the time ____ Most of the time ____ Some of the Time ____
A little of the time ____ None of the time ____

Ware and colleagues describe the calculation of the SF-12 physical and mental subscales[112].

INSTRUCTIONS FOR COMPLETING THE "MENQOL"

This questionnaire lists problems that some women might experience during menopause. Each of the items in the questionnaire is in the form of the examples belows;

Indicate whether or not you have experienced this problem in the *last month*.

Sweating Yes No	Not at all bothered	0	1	2	3	4	5	6	Extremely bothered

Go to the next item

If you *have not* experienced the problem: Mark "NO"

Sweating Yes No ☐	Not at all bothered	0	1	2	3	4	5	6	Extremely bothered

Go to the next item

If you have experience the problem:
Mark **"Yes"** then rate how ***bothered*** you were by the problem by circling one of the numbers.

Sweating Yes ☐ No	Not at all bothered	0	1	2	∠	4	5	6	Extremely Bothered

Go to the Next Item

This questionnaire is completely confidential. Your name will not be associated with your responses. However, if for any reason you do not wish to complete an item, please leave it and go on to the next one.

For each of the following items, indicate whether you have experienced the problem in the **PAST MONTH.** If you have, rate how much you have been ***bothered*** by the problem.

	Not at all Bothered	0	1	2	3	4	5	6	Extremely Bothered
1. Hot Flushes or Flashes	No Yes	0	1	2	3	4	5	6	
2. Night Sweats	No Yes	0	1	2	3	4	5	6	
3. Sweating	No Yes	0	1	2	3	4	5	6	
4. Being dissatisfied with my personal life	No Yes	0	1	2	3	4	5	6	
5. Feeling anxious or nervous	No Yes	0	1	2	3	4	5	6	
6. Experiencing poor memory	No Yes	0	1	2	3	4	5	6	
7. Accomplishing less than I used to	No Yes	0	1	2	3	4	5	6	
8. Feeling depressed, down or blue	No Yes	0	1	2	3	4	5	6	
9. Being impatient with other people	No Yes	0	1	2	3	4	5	6	
10. Feelings of wanting to be alone	No Yes	0	1	2	3	4	5	6	
11. Flatulence (wind) or gas pains	No Yes	0	1	2	3	4	5	6	
12. Aching in muscles and joints	No Yes	0	1	2	3	4	5	6	
13. Feeling tired or worn out	No Yes	0	1	2	3	4	5	6	
14. Difficulty sleeping	No Yes	0	1	2	3	4	5	6	
15. Aches in back of neck or head	No Yes	0	1	2	3	4	5	6	
16. Decrease in physical strength	No Yes	0	1	2	3	4	5	6	
17. Decrease in stamina	No Yes	0	1	2	3	4	5	6	

18.	Feeling a lack of energy	No Yes	0 1 2 3 4 5 6
19.	Drying skin	No Yes	0 1 2 3 4 5 6
20.	Weight gain	No Yes	0 1 2 3 4 5 6
21.	Increased facial hair	No Yes	0 1 2 3 4 5 6
22.	Changes in appearance, texture or tone of your skin	No Yes	0 1 2 3 4 5 6
23.	Feeling bloated	No Yes	0 1 2 3 4 5 6
24.	Low backache	No Yes	0 1 2 3 4 5 6
25.	Frequent urination	No Yes	0 1 2 3 4 5 6
26.	Involuntarily urinating when laughing or coughing	No Yes	0 1 2 3 4 5 6
27.	Change in your sexual desire	No Yes	0 1 2 3 4 5 6
28.	Vaginal dryness during intercourse	No Yes	0 1 2 3 4 5 6
29.	Avoiding intimacy	No Yes	0 1 2 3 4 5 6

Calculation of the MENQoL requires re-coding as follows: no = 1, yes = 2 to 8 with 2 corresponding to 0 on the bothered scale and 8 corresponding to 6.

The vasomotor subscale is calculated by adding questions 1-3 and dividing by 3.
The psychological subscale is calculated by adding questions 4-10 and dividing by 7.
The physical subscale is calculated by adding questions 11-26 and dividing by 16.
The sexual subscale is calculated by adding questions 27-29 and dividing by 3.