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Grant Application: Randomized Comparison of Two Internet-Supported Natural Family Planning Methods

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Statement of the Problem

Studies consistently show that women want safe, effective, easy to use, and convenient methods of family planning.[1-3] Although natural family planning (NFP) methods are free of side effects, they are often ineffective and complex to learn and use.[4-6] Efforts have occurred over the past 10 years to simplify the teaching and use of NFP methods and increase the efficacy.[3,4,7,8] These efforts include the development of low tech calendar-based methods[4], simplifying instructions[7,8], and developing accurate biological markers of fertility.[9-13]

A new high-tech electronic method to monitor fertility has recently been developed to help women determine their fertile window with ease, convenience, and accuracy.[3,14] This high-tech electronic hormonal fertility monitor (EHFM), called the ClearBlue Easy Fertility Monitor (Inverness Medical Innovations), measures urinary metabolites of estrogen and LH and provides the user with a daily indication of "low," "high" and "peak" fertility. A recent cohort study demonstrated that EHFM was effective when used as an aid to avoid pregnancy along with cervical mucus monitoring (CMM) as a second marker of fertility[15]and users reported high satisfaction with the method.[16,17] However, there are no randomized comparison studies of EHFM NFP methods with NFP methods that utilize traditional biological markers of fertility (i.e., the ovulation method and cervical mucus monitoring).[5]

Other recent efforts to increase the ease of use and convenience of NFP methods are the use of internet support for NFP instructions and automated online fertility charting.[18-20] Although there have been studies to determine the knowledge base of an online hormonal contraceptive program there have been no studies to determine the efficacy of internet-based instructions for NFP methods used to avoid pregnancy.[21] Nor have there been studies to determine the efficacy and satisfaction of using an online fertility charting system for NFP purposes.

A key component in the use of NFP or any type of behavioral focused method of family planning is the motivation of both partners in the use of the method to avoid pregnancy.[22] If only one of the partners is committed to the method it will be difficult to use and the efficacy will most likely be lower. Mutual motivation has been recognized in the family planning and, in particular the NFP community, as essential for NFP efficacy.[23] However, there have been no recent studies that have investigated this component for the use of NFP methods.

Therefore, the specific aims and hypotheses of this proposed study are as follows:

1. to determine and compare the efficacy in the use of two internet-supported methods of NFP (i.e., EHFM and CMM) in aiding couples to avoid pregnancy. **Hypothesis** - Those couples who use an internet-supported EHFM-aided NFP method will have fewer unintended pregnancies over a 12-month time period compared to couples who use an internet-supported CMM-only NFP method.
2. to determine and compare the satisfaction and ease of use in the use of two internet-supported methods of NFP (i.e., EHFM and CMM) in aiding couples to avoid pregnancy. **Hypothesis** - Those couples who use an internet-supported EHFM-aided NFP method (over a 12-month time period) will have greater satisfaction and ease of use compared to those couples who use an internet-supported CMM NFP method.
3. to determine and compare the mutual motivation in the use of two internet-supported methods of NFP (i.e., EHFM and CMM) in aiding couples to avoid pregnancy. **Hypothesis** - There will be fewer unintended pregnancies among couples who have high mutual motivation in the use of a NFP method to avoid pregnancy (whether EHFM or CMM) compared to those couples with low mutual motivation.

The research questions that will be asked are:

1. What are the 3, 6, and 12-month correct use and total use unintended pregnancy rates of an internet-provided EHFM-aided NFP method?

2. What are the 3, 6, and 12-month correct use and total 12-month use unintended pregnancy rates of an internet-provided CMM-only NFP method?

3. What is the satisfaction, ease of use, and mutual motivation of an internet-based NFP method (either EFHM or CMM) over a 12-month time period, i.e., after 1, 3, 6, and 12 months of use?

The innovations of this proposed study are: 1) the use of an internet-based Web site to provide NFP instructions and support, 2) the use of an electronic fertility charting system; 3) the use of a new simplified method of NFP that utilizes EHFM, 4) the randomized comparison of two methods of NFP, i.e., EHFM and CMM, and 5) the determination of mutual motivation on NFP efficacy. These aims and innovations address two of the research goals stated by the Office of Population Affairs and the Office of Family Planning: to identify strategies and factors that enhance the use and efficacy of NFP among family planning clients. To this end, this project is highly significant. What will be different as a result of your project? How will it advance the field? Why should your project be funded over others?

Background and Significance of Problem:

Unintended pregnancies are a major health problem for women in developed and developing countries.[24-26] In the United States (US), for example, approximately 50% of all pregnancies are unintended and almost half of these result in abortion.[27] Many of these unintended pregnancies are due to discontinuation of contraceptive methods, and in turn, discontinuation is often due to dissatisfaction with contraceptive methods -- and in particular with hormonal side effects.[25] On the other hand, natural family planning (NFP) methods are free of side effects (other than unintended pregnancy) and have very low discontinuation rates when compared to other methods of birth control.

However, relatively few women use NFP for family planning purposes. Based on the 2002 National Survey of Family Growth – a survey of the US National Health Statistics division of the Centers for Disease Control and Prevention-- there are only 124,000 women in their reproductive

years that use modern methods of NFP, i.e., temperature or cervical mucus based methods.[28] This represents only 0.2% of all US women between the ages of 15-44. Another 0.4% use calendar based or, most likely, self-devised calendar based methods.[28,29]

A recent peer-reviewed synthesis of the best efficacy studies has determined that NFP methods are somewhat ineffective in helping couples avoid pregnancy.[5] Major reasons cited as to why so few couples use NFP methods are: 1) NFP methods are relatively ineffective – average or typical use will provide approximately 20-25 unintended pregnancies per 100 women over a 12-month time period; 2) NFP methods are not all that easy to provide or to use; and 3) health professionals are reluctant to provide NFP services due to their inefficiency and poor efficacy. Only about 6-10% of physicians and advanced practice nurses in the US and Europe would consider prescribing them for birth control purposes.[30,31]

Insert a paragraph here that has a positive spin. Although NFP, as it presently stands, has its drawbacks, there are many advantages as well. If we can minimize the drawbacks, truly NFP can be a realistic and relatively inexpensive way of increasing the proportion of pregnancies that are intended, as well as improving health outcomes.

The following review will: 1) analyze evidence for the inefficiency and inaccuracy of current biological indicators of fertility used with current NFP methods, 2) describe perfect and typical use efficacy of new NFP methods, and 3) discuss efforts to increase the efficiency and efficacy in the provision of NFP services.

Inefficiency and Inaccuracy of Natural Biological Markers of Fertility

NFP methods provide the women users with the ability to estimate the fertile time in the menstrual cycle by the self-observation of natural biological markers of fertility. With information about fertility, a couple can decide to avoid or achieve a pregnancy through periodic abstinence (to avoid) or focused intercourse (to achieve) during the fertile time.

A man and woman together are fertile only for 6 days in the menstrual cycle. These six days are known as the fertile window. This time frame was confirmed by Wilcox and others in a classic study reported in a 1995 article in *The New England Journal of Medicine.*[32] The 6 days are based on the physiological knowledge that a human female egg is viable and capable of being fertilized only 12-24 hours after ovulation and that sperm will survive 3-5 days in a cervical mucus-enriched environment. NFP involves using natural biological markers to estimate the beginning, peak, and end of that fertile window.

The most common natural biological markers that women use to self-identify or estimate the fertile window in current systems of NFP include calendar-based formulas (determined by statistical estimates of when the fertile window will occur within the menstrual cycle), a rise in the woman's basal body temperature (BBT) as a result of the progesterone stimulated upward shift in body temperature after ovulation, the changes in cervical mucus and the cervix due to the influence of rising levels of estrogen from a ripening egg, and self measured threshold levels of estrogen and lutuenizing hormone (LH) in the urine with an electronic hormonal monitor.

BBT recordings have been widely used to indirectly predict ovulation for the purpose of avoiding and achieving pregnancy. BBT is still used by many physicians and nurses to help assess, diagnose, and treat infertility. While BBT is inexpensive and easy to use, it is often an imprecise predictor or indicator of ovulation.[10,33-34] About 10-20 % of ovulatory menstrual cycles will not show a bi-phasic shift in temperature.[33,34] Furthermore, the criteria for determining a temperature shift (i.e., 0.2, 0.3, or 0.4° F) and where that shift occurs in the cycle will vary considerably.[35] Body temperature can also rise due to other phenomena such as stress, disrupted sleep patterns and infection. Fortunately, other simple means of monitoring fertility have been developed to help women to predict and confirm the time of ovulation.

The self-observation of cervical mucus has been used by many women to predict and detect the approximate time of ovulation. Determining optimal or peak cervical mucus, unlike BBT, is

based on a pre-ovulatory and estrogen methodology. Estrogen, which stimulates the production of cervical mucus, rises in the serum before ovulation takes place. Optimal cervical mucus has been shown to correlate well with the serum and urine LH surge and the ultrasound determined day of ovulation.[13,36-40] The fertile period begins with the first day of observable mucus and lasts until three days past the last day of peak type mucus. The average amount of days from the first day of mucus until the peak day is 6.5 days.[41] Most algorithms for the use of cervical mucus monitoring in natural family planning (NFP) add a three-day count after the peak day. [20,42-43] These three days along with 6.5 in front of the peak day and 2-3 days of menses produces on average a 12 day fertile period, 6 days more than is necessary.[41]

Some researchers claim that observing cervical mucus, although useful in monitoring fertility, does not accurately predict or confirm ovulation.[10,44-45] About twenty percent of women experience a continuous mucus discharge throughout their menstrual cycles and find it difficult to distinguish the optimal fertile mucus. Although most women with a continuous discharge can eventually determine their peak, this takes a considerable amount of time, patience, and the assistance of a knowledgeable practitioner or teacher—a particularly frustrating experience for women/couples who have infertility problems and are trying to achieve pregnancy. This frustration was confirmed by Italian researchers who discovered that the fertile phase as estimated by cervical mucus is approximately 17 days in length.[46,47] Furthermore, when master teachers of the NFP retrospectively estimated the days of fertility on cervical mucus only charts, the correlation between the ratings of the master teachers was only 60%. Yet, when using a cervical mucus only method the woman user is expected to prospectively estimate fertility with the same markers. A simple, objective and accurate test to predict and detect ovulation would greatly help women with continuous cervical mucus as well as increase the effectiveness of natural methods of fertility control and awareness.

Detecting the LH surge in the urine is considered by experts to be a standard method and one of the best tests for indirectly self-predicting ovulation.[34,48-49] Ovulation detection kits have been developed employing monoclonal antibody technology to detect the LH surge that occurs in the urine 12-24 hours before ovulation.[50] The manufacturers of ovulation test kits claim a greater than 99% accuracy in detecting the LH surge. However, the test kits miss the LH surge or do not detect the surge in about 10% of cycles.[51] The LH surge in the urine does not give a long enough warning period before ovulation takes place in order to be used for avoiding pregnancy and frequently misses the two most fertile days in the cycle.[52] Test kits need to be purchased for each menstrual cycle and thus will be a monthly expense.

The Clearblue fertility monitor (CBFM) is a significant new development in the prediction and detection of ovulation. The Clearblue monitor consists of a hand-held digital monitor and disposable wick-type test sticks. The monitor identifies a woman's fertile period by identifying a threshold level of estrone-3-glucuronide (E3G), the urinary metabolite of estradiol and by identifying the urinary surge of luteinizing hormone (LH). The CBFM reads the test sticks to detect changes in the hormone levels and provide the user with a reading of " low," "high" and "peak" fertility. At a minimum the monitor usually will give the user at least one day of "high" fertility and two days of "peak" fertility. However, in very few women the day of the estrogen rise coincides with the day of the LH surge. The user therefore goes straight from "low" to "peak." In addition some women may only see "low" and "high" signals, particularly if they miss tests or have an infertile and anovulatory cycle. The "high" reading is triggered by a threshold level of urinary estradiol and the "peak" of fertility by the urinary surge of LH.

The CBFM is currently sold and marketed only for women who wish to track their fertility and achieve a pregnancy. However, the information provided by the monitor could be used inversely for avoiding pregnancy. As mentioned, the monitor at a minimum provides the user with one day of "high" fertility and two days of "peak" fertility.[14] In greater than 70% of the

cycles, the monitor will provide 5 or more days of "high" and "peak" fertility and in 85% 4 days or more. If a user avoids intercourse during the "high" and "peak" fertility days and at least one day after, there should be less than a 30% chance of pregnancy using the monitor alone. This is because sperm live 3 days in good cervical mucus and in rare cases up to 5 days and once a woman ovulates she is only fertile from 12-24 hours. So at a minimum the fertility monitor alone provides the user with a 1-3 day warning before ovulation takes place.

In a recent study of the CBFM, ovulation, as detected by ultrasound, occurred 91.1% of the time during the 2 "peak" days on the monitor and 97.0% during the two "peak" days plus one (i.e., the high day after the peak) in 135 of 149 ovulatory cycles.[11] There were no detected ovulations before the monitor "peak" days. It was also found that in 92% of the cycles, the first "high" reading coincided with the serum estradiol rise day. A recent study by Tanabe, Susmu and Hand, et al with 30 healthy volunteer women showed that the CBFM provided up to 5 days of "high and peak " fertility days in 58.6% (N = 17) of the cycles before the urinary LH peak.[12] They concluded that the device will allow couples to use the information to time intercourse for the best prospects of achieving pregnancy. However, it remains to be seen whether the advanced warning of peak fertility will result in intercourse and increase the chance of conception.

In summary, all of the current indicators of fertility utilized in methods of NFP are imperfect. All produce information regarding menstrual cycles that is hard to interpret. Most of these indicators overestimate the actual fertile phase. However, new technology that allows a woman to measure reproductive hormones (rather than a bodily response to them) and that provides an objective reading is a breakthrough for woman with serious reasons to avoid pregnancy and who wish to use NFP. However, there is little evidence to show that the use of EHFM for NFP purposes is more effective than traditional less expensive methods of NFP.

Efficacy of NFP

When reporting efficacy of methods of family planning to avoid pregnancy, two numbers are provided: the correct use efficacy and the total use efficacy.[6] The correct use (also called perfect use**)** unintended pregnancy rate refers to those pregnancies that occur when the method is used consistently and according to instructions. The total pregnancy rate includes the combination of both unintended pregnancies when the methods are followed correctly and the unintended pregnancies that occur when users of the method do not always follow the instructions of the method correctly and consistently. Typical use rates are also used and refer to the average rate in the use of the method outside of a controlled efficacy study. Typical use and total use pregnancy rates are sometimes used interchangeably in the literature.

According to Trussell, NFP methods have a very low perfect use unintended pregnancy rate of 1-3%, but fairly high (i.e., 20-25%) typical use unintended pregnancy rate, a rate that is higher than condom use which is also a behavioral method.[6] He also refers to NFP methods as "unforgiving" in that if a couple has intercourse during the fertile phase they most likely will get pregnant. It should be noted that, the correct and total use unintended pregnancy rates of NFP methods can be deceiving. For instance, the more days that a particular method indicates are fertile in a menstrual cycle, the more likely that that method will have a low correct use rate but a high total unintended pregnancy rate. An example is the "mythical method" of NFP that indicates the only days of infertility are the first and last days of the menstrual cycle. This method will have a very low (next to nothing) unintended pregnancy rate with perfect use, i.e., avoiding having intercourse on all but the first and last day of the menstrual cycle. However, it will be difficult for the general population to use, because it has an average of 26 days of fertility. Because of the difficulty in using such a method, there will be a high incorrect use and high total pregnancy rate. Few couples would want to avoid intercourse an average of 26 days per menstrual cycle and have only two days available for intercourse. A similar situation occurs with the current methods of NFP. For example, with the cervical mucus only methods of NFP, 40-

60% (on average) of the menstrual cycle is considered fertile. It will be difficult to achieve an unintended pregnancy with perfect use of these methods. However, because these methods are somewhat difficult to use (i.e., the instructions and the interpretation of the cervical mucus signs are not always easy, and there are many days of "estimated" fertility), the typical unintended pregnancy rate will be high. On the other hand, more accurate methods with shorter estimated fertile phases might have higher perfect use rates but lower typical use unintended pregnancy rates, especially if the methods are easy to understand and use.

Table 1 shows the perfect and typical use rates of the most recent NFP efficacy studies that have been published in peer reviewed journals, in addition to a large classic (5 country study) of the ovulation method conducted by the World Health Organization (WHO).[3,4,7,53-58] The WHO[53] study analyzed the efficacy of the cervical mucus only ovulation method, the Howard, et al.,[54] study evaluated a standardized type of cervical mucus only method, the first Arevalo, et al.,[4] study evaluated the efficacy of a fixed day calendar based method, the second Arevalo, et al.,[7] study determined the efficacy of a simplified cervical mucus only study, the Frank-Herrmann, et al.,[2] study analyzed the efficacy of a European temperature plus cervical mucus plus calendar formula, the first Fehring, et al.,[55] study determined the efficacy of a combination of cervical mucus plus EHFM, and the second Fehring, et al.,[56] determined the retrospective efficacy of a combination of either cervical mucus observations, basal body temperature, and/or the use of the EHFM. These studies included only women with regular menstrual cycle lengths. The Arevalo, et al.,[7] and the two Fehring, et al.,[55,56] studies having the most liberal length of 13-42 days. The total unintended pregnancy rate of the WHO study of 22% is the highest.[53] The Frank-Herrmann, et al.,[3] European double check method has the lowest total rate, similar to that found with oral hormonal contraceptives.

Table 1: Classic and Recent NFP Efficacy Studies: Correct Use and Total Survival Rates* per 100 Women Over 12 Months of Use

Study	Indicators	Length**	Correct	Typical
WHO[53]	Mucus	**(25-32)**	**97**	**78**
Howard, et al.[54]	Mucus	**(25-32)**	**100**	**86**
Arevalo, et al.[4]	Fixed Calendar	**(26-32)**	**95**	**88**
Arevalo, et al.[7]	Mucus	**(13-42)**	**96**	**86**
Frank-Hermann, et al.[2]	Mucus & Temp	**(25-35)**	**99**	**92**
Fehring, et al.[55]	Mucus/E3G/LH	**(21-42)**	**98**	**87**
Fehring, et al.[56]	Mucus/Temp/LH	**(21-42)**	**99**	**89**

* Survival rate = percent of women per 100 that did not have an unintended pregnancy.

** Range of length of menstrual cycles in study.

The unintended pregnancy rates jump considerably with use of NFP methods when other than regular cycles (i.e., including post pill, post-partum, and peri-menopause) are included in the calculations. For example in the Howard, et. al.,[53] study, the total unintended pregnancy rate of a cervical mucus only method jumps to 17%, and a data base of the same method from Marquette University indicates the CMM only method rate is approximately 22% -- similar to the WHO study rate – when all unintended pregnancies are included from all reproductive categories.

In summary, NFP methods are fairly effective when the rules of the methods are followed consistently and when used by women with fairly regular length menstrual cycles. Efficacy suffers when the methods are not used consistently and when used by women with irregular

menstrual cycle lengths (especially during post-partum and breastfeeding). It remains to be seen whether an EHFM method of NFP is more effective than another traditional method.

Efficient Methods of NFP/FAM

This section describes recent efforts to streamline NFP methods and make them more user and provider friendly (and yet maintain efficacy). Researchers recently developed a simple fixed day (or what they call the standard days method (SDM)) whereby days 8-19 are always considered fertile.[4] The method is for women who have menstrual cycles between 26-32 days in length. They method was implemented with a simple system of colored beads (called Cyclebeads) that indicate the days of fertility with white beads and the infertile days with brown beads. A three country efficacy study found a correct use unintended pregnancy rate of 5% and a typical use rate of 12%. Another simple NFP method developed by the same researchers is the Two Day method.[7] This is a simplified version of the cervical mucus only method that entails asking two questions: 1) did I notice any secretions today?, and 2) did I notice any secretions yesterday? If the woman answers "No" to each question she can consider herself as infertile. These researchers also published an efficacy study of this method among couples from three countries and found a typical use rate of 14%.

European physicians and scientists took on the task of creating an efficient and accurate method of NFP for busy European women who wanted a secure natural method of birth control.[2] They studied the various markers and rules of current NFP methods and developed what they call the double check method of NFP, i.e., a double check symptom-thermal method. The double check for the beginning of the fertile phase is the presence of cervical mucus and/or a calendar based formula; the end of the fertile phase is the peak in cervical mucus or the BBT temperature shift (whichever comes last). A recent prospective efficacy study among 900 couples provided efficacy rates for this method that rival the hormonal birth control pill. This study emphasized that having two measures to estimate the beginning and end of the fertile phase seems to add

rigor to the method -- at least among motivated women who are consistent in following the instructions of the method.

Project Design:

At Marquette University we developed what we call the Marquette Light method of NFP that can be taught initially in a 12-minute office session. The method uses either cervical mucus or an EHFM and a calendar-based formula as a double check for the beginning and end of the fertile phase. Whether the woman user observes cervical mucus or uses the CEFM, she rates her fertility as being low, high, or peak, and utilizes the same fertility calendar-based formula for a double check. This simplified method needs to be evaluated for its efficacy.

Besides simplifying the use and provision of NFP methods, there have been efforts to integrate information technology into the use and provision of NFP services, particularly the use of the internet. In the United States there are a number of Web-based programs that provide information on how to use NFP methods. These include the Northwest Family Services which teaches a multiple fertility indicator method (i.e., cervical mucus and basal body temperature), the Franciscan system cervical mucus method being developed by a physician and nurse practitioner team in California, and the Ovusoft system developed by Weschler, the author of the book "Taking Charge of Your Fertility".[20] The Ovusoft system is the most widely used software system for tracking fertility. It is also used as an online charting system.

Researchers and NFP providers at Marquette University recently developed an online system to teach couples to use NFP. The need to develop such a system was a result of experiences n providing NFP over the past 5 years. Couples are often reluctant (or too busy) to come to an onsite setting for in-person NFP services and often do not show up for appointments. Furthermore, the researchers received e-mail requests to learn NFP via e-mail on a weekly basis. It was determined that an online service system for NFP would be more efficient in being able to

reach people around the world without leaving their homes or place of work and more efficient that constantly sending the same information as attachments to e-mail messages.

The Marquette online NFP services are currently being piloted with 50 couples. The NFP Web site (http://nfp.marquette.edu) has free information on NFP, downloadable charting systems, access to protocols for special circumstances (e.g., using NFP while breastfeeding), and instructions for achieving and avoiding pregnancy. A unique aspect of the information section of the Web site is a one-page simple Quick Start Instructions that can be read in five minutes and allows the user to begin charting and using NFP.

Couples who register on the Web site are able to access an electronic charting system, discussion forums, and receive consultation from professional nurse NFP teachers and an obstetrician gynecologist with expertise in the use of NFP. The online charting system also notifies the user of possible health problems, including unusual bleeding, infertility, and cycle dynamics that are out of the norm. The Marquette online NFP system is in both the English and Spanish languages. However, none of these systems has been studied for its efficacy and ease of use. Furthermore, the efficacy of these systems will only be as good as the NFP method that they provide.

Conceptual Framework: Acceptability and Mutual Motivation

Acceptability, ease of use, and motivation are important components for successful use of NFP methods.[23] Researchers recently assessed the acceptability of using EHFM with 220 women who recorded their acceptability and ease of use of the fertility device.[57] They concluded that the fertility monitor was highly acceptable to volunteer couples and that the monitor had a positive effect on the women's reproductive functioning, the women's health, and the couples' relationships. In a related study, researchers conducted a study to determine the psychological impact of using a EHFM with 52 couples from Florida and North Carolina.[58] Acceptability of the monitor and having fertility-focused intercourse were more favorable at

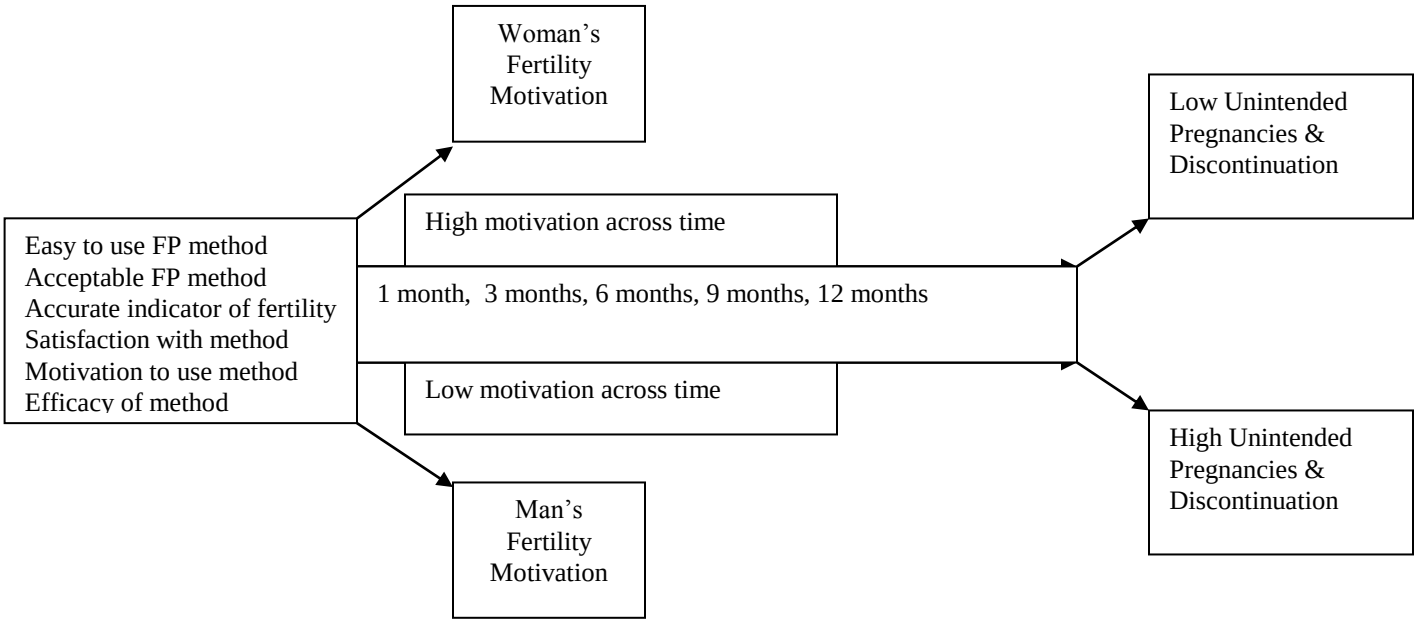
baseline among the couples who eventually achieved a pregnancy. These same researchers also reported on the acceptability of the use of EHFM in a longitudinal study of 608 English women users willing to avoid pregnancy for at least 15 months.[59] The authors concluded that the participants, in terms of initial acceptability of the fertility monitor, were very positive and that acceptability (i.e., perceived accuracy and trust) became more positive over time. There have been no studies to determine the acceptability and ease of use of the CBFM as a device to monitor fertility and avoid pregnancy along with a double-check of the fertile window (i.e., a fertility algorithm).

A recent study was conducted to determine the strength of motivation and ambivalent fertility desires among women in Sub-Sahara Africa and to suggest strategies to meet population-based unmet family planning needs.[60] The authors concluded that it was important to assess the strength of fertility motivation when determining which women have unmet family planning needs and suggested a systematic screening algorithm to identify these women. NFP teachers have long known about the importance of motivation and whether the NFP couple/client users are either delaying or limiting family size. Including a screening algorithm within a NFP service program that assesses motivation and intention for avoiding or achieving pregnancy is important.

Researchers recently conducted a study to determine characteristics that might predict incorrect use of a NFP method.[61] The women participants for this were 928 women from 10 different sites in four countries (i.e., Bolivia, Guatemala, Peru, and the Philippines). Of these 928 women, 212 (23%) reported at least one act of intercourse during the estimated fertile phase in at least one menstrual cycle, i.e., they practiced incorrect use of these methods. Most (39) said they had intercourse on fertile days because their husbands insisted. Others (18) felt that the length of abstinence and the fertile period were too long, and 15 of the women felt the daily routine of the methods was too difficult. This study illustrates the importance of mutual motivation, ease of use, and efficiency in NFP methods to be successful.

For this study the Model of Mutual Fertility Motivation (MMFM) will be utilized as the conceptual psychological base for this study.[62] The MMFM combines the individual level of fertility motivation with the couple level of fertility motivation and realizes that these differ and change over time. Furthermore, this model takes into consideration the incremental behaviors that are designed to promote or prevent childbirth. This model also stipulates that motivation entails communication, influence, and disagreement on fertility desires between partners and that these dynamics will influence motivation to use or not use a method of family planning. Little research has been conducted with NFP methods to determine the effect of mutual partner motivation on NFP efficacy. This study will do so by including a simple and repeated measure of motivation, i.e., fertility intention and strength of intention by both partners across the time of the study, i.e., before each menstrual cycle of charting for up to 13 cycles of use. When there is concurrence in motivation and when there is high motivation to avoid pregnancy by both partners, then behavioral methods of family planning, and in particular NFP will be more effective. Other factors such as ease of use, satisfaction, and efficacy of the method of NFP are important as well. See mapping of model below.

Mutual Motivation Fertility Model



D. Research Design and Methods

Research design. This will be a 12-month (13 cycles) prospective randomized clinical efficacy trial of the EHFM plus fertility algorithm method of NFP in comparison with the CMM plus algorithm method of NFP. A minimum of 600 couples seeking to avoid pregnancy with a method of NFP and who have no known infertility problems will be sought through an online NFP web site and randomized into either a EHFM group (N=300) or a CMM only group (N=300). Any pregnancies that occur among the participants over a 12 month period will be recorded and evaluated as to whether they were intended, not intended user failure, not intended system failure, or unknown. Pregnancies will be confirmed by a positive urine pregnancy test and a luteal phase longer than 18 days. All couple participants (men and women) will be assessed as to their perceived "satisfaction" and "ease of use" with an online measurement tool at 1, 3, 6, and 12 months of use. Mutual motivation for avoiding pregnancy will be assessed before each menstrual cycle.

Sample. In order to reach a significant level of analysis for a comparison of pregnancy rates between two groups, i.e., EHFM and CMM group, a minimum of 600 women/couple participants will be sought for completion of the study. In order to achieve 80% power to detect a 10% difference in pregnancy rates between each group there needs to be a minimum of 300 couples per group. This power analysis is based on a total unintended pregnancy rate of 10% for the EHFM group and a 20% pregnancy rate for the CMM group. These rates were projected from the preliminary retrospective study that compared the CMM only method with an EHFM method.

An additional 150 couples will be sought as an over sample and to ensure that enough participants will complete the study, i.e., 75 participants for each group. The over sampling of 150 participants is based upon the typical discontinuation rate for modern methods of FAM of

approximately 25%. Therefore, 600 women or 1200 (women and their male partner) participants will be purposively sampled from couples who seek to enroll in an online NFP course.

Couples who seek the online NFP services and meet the criteria for the study will have the opportunity to participate in the study. Randomization will take place by having a computer generated pre-randomization list of numbers from 1-500. As couples meet the criteria for the study and consent to participate, they will be assigned to either the EHFM or CMM group as indicated by the pre-randomization list. All couples will receive a free EHFM but those in the CMM group will receive the monitor only after completing 12 months of CMM. All couples will receive $10 for each menstrual cycle chart completed. This reward will help cover the cost of test strips and serve as a motivation to continue with the study. If a couple refuses to participate because they want to be in the EHFM group they will be told that they are not eligible.

Inclusion criteria for female participants. The female partner who wishes to avoid pregnancy must: be between the age of 18 and 42; have a menstrual cycle range of 21-42 days; have not used depo medroxyprogesterone acetate (DMPA) over the past 6 months; have no history of oral, patch or sub-dermal hormonal contraceptives for the past 3 months; if post breast-feeding, have experienced at least 3 cycles past weaning; have no known fertility problems; not be using medications that interfere with ovulatory function; not smoke cigarettes; and not be pregnant. The potential participant will also need to be open to a possible pregnancy and be able to read and understand written English or Spanish at the 9th grade level.

Inclusion criteria for male partners. Male participation in the study will also be required. Male partners are to have no known fertility problem and be between the ages of 18 and 50. Most husbands and partners of NFP couples are actively involved in learning and using natural methods of the ovulation method. They will participate in the online training of fertility monitoring and be asked to complete the satisfaction, ease of use, and motivation surveys. They too will need to be able to read either English or Spanish at a 9^{th} grade level.

Settings. The physical setting of the study will be the Marquette University College of Nursing Institute for Natural Family Planning. The Marquette NFP clinic is housed in private offices at the Marquette University College of Nursing. Marquette University College of Nursing has been providing professional NFP services since 1985. We recently initiated an online service program to provide NFP services and currently have 50 couples enrolled in a pilot study. The Marquette NFP Web site will serve as the digital online setting for this study.

Measures:

1. Measurement of the fertile period by the Clearblue Fertility Monitor (CBFM). The CBFM is designed to detect the rising level of urinary estrone-3-gluconuride (E3G) and the surge in urinary LH. The CBFM is based on urinary hormonal immunoassay techniques. Product testing has shown the Clearblue monitor to be 98.8% accurate in detecting the LH surge.[64] The CBFM detected the LH surge in 169 of 171 cycles from 88 women, in agreement with a quantitative radioimmunoassay for LH. Detection of urinary metabolites of urinary estradiol (E3G) has been recognized by the World Health Organization (WHO) as a reliable marker for the beginning of the fertile phase of the menstrual cycle. In a study with 90 women who used the CBFM for 1-4 cycles, in 352 cycles with an LH surge, the first day of High Fertility (i.e., the day of the first rise in E3G) was 3.01 ± 2.33 days before the LH surge.[14,64]

The CBFM is initiated when the user pushes a button on the monitor labeled "M" on the first day of her period. The monitor then indicates which day of the cycle the user is on. The monitor requests either 10 or 20 daily urine tests per cycle. When the monitor requests a test, the user places the test strip under her urine stream for 3 seconds. The test strip is then placed in the monitor and read. The monitor will show a fertility status of "low," "high" or "peak." The user will be asked to record on the electronic NFP fertility chart her fertility status (low, high or peak) and any intercourse that occurred on a daily basis.

2. Measurement of the fertile period by cervical mucus monitoring (CMM). For this study, cervical mucus will be self-observed and classified at three levels -- low, high, and peak. Observations will be based on sensations and appearance of cervical mucus. When no mucus is observed or felt, or mucus that is slightly moist and sticky, minimal, thick, white, and holds its shape, will be classified as "low" fertile mucus. Mucus that feels wetter, increases in amount, becomes thinner, cloudy and slightly stretchy will be classified as "high" fertility mucus (this mucus can be considered transitional). Any mucus that feels slippery, is abundant, thin, clear, and stretchy (like egg white) will be classified as "peak" type mucus. The peak day is the last day of peak type mucus.

Women who are in the CMM group will be asked to observe for cervical mucus on a daily basis and to chart the highest level observed. They will be instructed to feel for the sensation of cervical mucus (at the vulva) throughout the day and especially when voiding and before going to bed. They will also be asked to observe any mucus at eye level by lifting it off a tissue and testing it between their fingers. Written, oral, and visual descriptions (pictures) of the three levels of cervical mucus will be provided to the CMM users. These are standard procedures utilized in CMM NFP methods and utilized in the World Health Organization (WHO) multi-site, multi-country study of the OM (WHO, 1981).[53]

3. Marquette Online Charting System. The Marquette University NFP online electronic charting system has designated sections for recording the results of CMM and the EHFM – as either L = low, H = high, or P = peak. The charting system provides a pop-up window for the user that illustrates the 3 levels of cervical mucus and the 3 levels provided by the fertility monitor. The charting system also has a place to record menses on a scale of 1-3 with 1 = light; 2= moderate; and 3=heavy menstrual flow and a row for recording acts of intercourse (= I). The top of the chart has room for recording intention of use (to achieve

or avoid pregnancy) for each cycle. The charting automatically indicates (in light blue) the fertile phase (based on the Marquette algorithm) as the user charts. There is no guessing as to whether the day is either fertile or not.

4. Classification of pregnancy: The electronic charting system automatically notifies the user of the possibility of a pregnancy when the luteal phase goes beyond 19 days. The charting system will then prompt the user to take a pregnancy test and complete an online pregnancy evaluation. The online charting system will also cue the woman user to a link that launches a pregnancy evaluation form on each menstrual cycle that is charted.

Two professional nurse NFP teachers will evaluate all pregnancies that occur among the participants. The NFP teachers will review the charting system for the days of fertility, the days of recorded intercourse, and the information on the pregnancy evaluation form. Each couple that achieves a pregnancy will be asked to confirm the pregnancy with a pregnancy test kit (i.e., the ClearBlue Easy One Minute Pregnancy Test). Each couple participant will be asked to record on their fertility chart before each new cycle of charting their intention of either achieving or avoiding pregnancy and their level of motivation for avoiding a pregnancy. A determination will be made if intercourse occurs during the fertile time as designated by the monitor and fertility algorithm. Each pregnancy will be classified (with agreement of the couple) by two professional nurse NFP teachers according to the following classification as recommended by Lamprecht and Trussell:[65] 1) pregnancies will be classified as intentional only when a couple reports prior to the pregnancy cycle an intention to use the method to become pregnant, 2) all unintentional pregnancies be used in the analysis of pregnancy risk during typical use, and 3) all unintentional pregnancies occurring during cycles in which NFP rules were followed will be used in the analysis of pregnancy risk during correct use.

5. Classification of discontinuation. All couples that discontinue from the study before it is complete will be recorded and classified as to why with the use of the Marquette University Institute for Natural Family Planning Discontinuation Form. This one-page 5-item form was adapted from the discontinuation form developed by Gray and Kambic.[66] The 5 items include date of discontinuation, the kind of discontinuation, whether lost to follow-up, health and medical reasons, and personal reasons. The "kind of discontinuation" include "lost to follow-up," "health related," "personal," "pregnant," and "other: specify." This information will be obtained upon discontinuation either in the online Web site or by e-mail.

6. Determination of satisfaction and ease of use. Satisfaction in the of use of the online NFP Web site will be measured by asking the woman participant and her male partner at one month, 3, 6, and 12 months of use their satisfaction of the methods on a scale of 1 = not satisfied, 2 = somewhat satisfied, 3= satisfied and 4 = very satisfied. They will also be asked to respond to a 10 item questionnaire on whether the online Web site was acceptable, easy to use, non-invasive, a convenient in-home test of fertility, and provides clear and objective results. The 10-item survey is a shortened form of an acceptability/ease of use questionnaire developed by Severy for evaluating an EHFM.[57] The 10 items are ranked on a scale from 1 to 7, with bipolar negative and positive adjectives. This is the same tool that was used in the prospective efficacy study of the EHFM plus CMM.[55]

7. Motivation. Motivation will be measured by the same system developed for the 2002 (cycle 6) National Survey for Family Growth.[67] There will be two questions asked of participants (the woman and man) i.e., 1) how hard they are currently trying not to get pregnant on a scale of 0 – 10, with 0 means trying hard to get pregnant and 10 means trying hard not to get pregnant, and 2) how much they want to avoid pregnancy at this time, with 0 means wanting to get pregnant and 10 means wanting to avoid pregnancy. In order to be rated as a High motivated couple they (i.e., the woman and her partner) need to have a score of 6 or better on the two motivation questions.

Both the woman user and her partner will be asked to rate their motivation levels before each menstrual cycle of use.

8. Demographic information. Each couple (male and female participant) who enters the study will fill out a 21-item demographic registration form developed by Gray and Kambic.[66] The registration form asks demographic information (e.g., ethnicity, religious status), number of children, cycle history, family planning history, and intention for using NFP. The registration form automatically pops up on the NFP Web site when the couple registers. They will not be able to enter into the system until the demographic form is filled out.

Procedures.

1. Web site modifications: The Marquette NFP web site will be updated based on the current running pilot study and to prepare for this proposed prospective randomized efficacy study. A special Web site will be developed by the Principal Investigator that announces the study, the purpose, and provides information on how to enroll into the randomized study. The current online Marquette NFP Web site will be modified to include the satisfaction, ease of use, and motivation tools, the reminder prompts for completing the tools, and a 15-minute video clip of a NFP introductory session. The NFP Web site will also need to include an online consent form. The nurse and physician providers involved in this grant proposal will already have experience with the Marquette NFP web site but will be updated to the changes

2. Recruitment of participants. Recruitment of 750 couples will take place over a 2-year time period. Participants will be recruited primarily through Web site advertisement, e-mail and regular mail contacts with Title X Region Coordinators, Title X providers, Diocesan NFP providers, and NFP list serves. The advertisement will include the criteria for participating in the study and the benefit of receiving a free EHFM. Advertisements will be placed online every month in key family planning web sites, diocesan web sites, and NFP lists. The current Marquette NFP Web site obtains about 25 participants per month without any advertisement.

3. Teaching couples CBFM or CMM NFP. Couples who meet the study criteria will be informed on the Marquette NFP Web site as to which group they have been randomly assigned. Those who were assigned to the EHFM group will be provided a voucher number for an online purchase of a fertility monitor. All of the participants will be then directed to listen and watch a 15-minute introductory session on NFP and provided Quick Instructions as to which method they will be using. The content of the slide show includes a definition of NFP, a brief explanation of reproductive anatomy and physiology, a description of the fertile window and the variability of the fertile window, how to use the EHFM or how to monitor and rate cervical mucus, how to chart fertility with the Marquette fertility charts, and how to use the algorithm to determine the fertile phase for avoiding pregnancy. They will then be asked to read the one-page Quick Instructions which tells them how to determine the beginning and end of the fertile window based on the method to which they were assigned. They also will be provided with brief instructions on how to use the online charting system – however, the current online charting system is intuitive.

After one month of charting, all participants will be prompted to complete the online satisfaction and ease of use questionnaires. They will again be prompted to complete these questionnaires at 3, 6, and 12 months. Those who delay in filling out the questionnaires or the online charting will be provided with a gentle e-mail prompt to do so. All participants will be encouraged to contact the online NFP teacher by e-mail if they have any concerns or questions. Couples in the CMM group that complete each questionnaire and provide one year of charting will receive a free CBFM at the completion of the study. Couples in either group will receive $10 for each complete menstrual cycle of charting. If any couple indicates the intention to have a pregnancy, they then have removed themselves from the study.

Evidence upon which the Analysis will Rely:

Researchers at the Marquette University (MU) Institute for NFP have conducted a series of studies that have an impact on this current proposal. First of all, a study was conducted that compared the estimation of the fertile phase of the menstrual cycle by the EHFM with self-observation of cervical mucus and found that CMM often over estimated the fertile phase and the EHFM underestimated the fertile phase.[63] The MU researchers then conducted a series of efficacy studies on the use of EHFM as an aid to CMM as a method of NFP. The first study was a prospective efficacy study and found that the method when used correctly is an effective fertility awareness based method of avoiding pregnancy (i.e., 3% correct use unintended pregnancy rate).[55] However, using both cervical mucus and the fertility monitor was rather complex to teach and use. This study also involved assessing the ease of use of the EHFM.[17] Overall ease of use, information provided, and the ability to use the monitor to avoid pregnancy were ranked very high by both partners. What is not known is how the ease of use and acceptability of the EHFM-aided method of NFP compares with a CMM only method.

The MU researchers then conducted a 12 month retrospective evaluation of the Marquette system of NFP and found the 12 month correct use pregnancy rate was 0.6 and the typical use (total pregnancy rate) was 10.6 per 100 users.[56] These rates were lower than the prospective study. As with the previous study, it was concluded that when used correctly the CMM system of NFP is a very effective means of avoiding pregnancy. This study was followed up with a retrospective cohort study comparing the unintended pregnancy rates of two methods, i.e., a cervical mucus only method versus a cervical mucus method with EHFM as a double check for the beginning and end of the fertile phase. The correct use rates were similar between the two methods (around 1-3%), but the total unintended pregnancy rates (13% for the EHFM method vs. 23% for the cervical mucus only method) were statistically different. The conclusion was that the use of hormonal monitoring as an objective double check for estimating the fertile window will

help lower the unintended pregnancy rate. However, the evidence is thin. There is a need for randomized clinical trials to know this with more confidence.

Analysis of Evidence:

The information from the online registration form, the online acceptability, ease of use, and motivation surveys, the online data charts, and the pregnancy evaluations will be entered into a computer data set (by a research assistant) in order to be analyzed with the Statistical Analysis System (SAS) and the Statistical Package for the Social Sciences (SPSS) software systems. Demographic data including age, number of children, education level, and cycle history will be analyzed and presented in descriptive form. All statistical analysis will be carried out using significance level alpha = 0.05. The data generated for the specific aims of this study will be analyzed as follows:

1. In order to determine the effectiveness of the EHFM plus a fertility algorithm in aiding couples to avoid pregnancy and the CMM plus a fertility algorithm in avoiding pregnancy, cumulative pregnancy rates will be calculated by (Life Table) survival analysis utilizing a 95% confidence interval:
    a. cumulative correct use unintended pregnancy rates will be calculated at 3, 6, 9, and 12 months/13 cycles of use.
    b. cumulative typical use (gross) pregnancy rates (of all unintended pregnancies) will also be calculated at 3, 6, 9, and 12 months/13 cycles of use.
2. To compare the effectiveness of the EHFM with the CMM in helping women avoid pregnancy, a Fisher non-parametric test (with a significance level of .05) will be calculated on the frequency of unintended pregnancy both correct use and typical use pregnancies.

3. Life Table analysis will be utilized to determine the discontinuation rates by couples using the CBFM and the CMM. The discontinuation rates will be recorded as frequencies and percents, and include the sub-categories of: lost to follow-up; health related; personal; pregnant; and other. Comparison of discontinuation rates will be calculated by use of chi square analysis to determine differences in frequency of discontinuation between the two groups.
4. Acceptability, ease of use, and motivation will be described using graphs and summary statistics such as frequencies, percentages, and means. Changes across time, differences between the EHFM and the CMM group mean scores of the acceptability, ease of use, and motivation tools will be analyzed using mixed model with repeated measures. While time, group, and question domain will be considered as fixed effects, subjects will be included in the model as random effects. If there is an indication of significant differences in certain fixed effects, Tukey's multiple comparison procedure will be used to find where the differences lie.

Secondary analysis will be performed to determine what day(s) intercourse took place in cycles that result in an unintended pregnancy and the probable reason for the pregnancy, i.e., unknown, teaching error, user error, etc. Regression analysis will be used to analyze the effect of the demographic factors on predicting acceptability score defined as the total score on the Acceptability/Ease of Use tool. Frequency of intercourse will be tracked and graphed across time within the 2 treatment groups (i.e., the CBFM and CMM groups) and compared between groups through the use of chi square analysis. The mean length of the fertile phase between the CBFM and CMM will be compared using 2-sample student *t* tests.

Limitations. A limitation of the study is that only healthy young women with fairly regular menstrual cycles (i.e., menstrual cycles with lengths between 21 and 42 days) will be tested. For the EHFM-aided method of NFP to be useful, further testing of women in a variety of

reproductive categories (e.g., breastfeeding and peri-menopause) will be necessary. Furthermore, the participants will have to have internet access and be familiar with computers. Another limitation is that the actual pregnancy rates will probably be lower than experienced in "real" life situations since the subject participation rewards will act as a motivation to comply with avoiding pregnancy and abstaining from intercourse during the fertile phase of the cycle. Furthermore, the unintended pregnancy rates will rely on the honesty of the couples reporting the time of intercourse and genital contact. There is a tendency to underreport genital contact and withdrawal with use of NFP methods. Finally, since both groups of couples will be exposed to the NFP system that the other group will be using (in advertisements, consent forms, and at the introductory session) they might have some bias that the other method of NFP is better or worse.

Staff and Qualifications:

The staff of this proposed research project

E. Human Subjects Protection

1. IRB and Compliance Approval. This study will be submitted for full review and approval from the Marquette University Institutional Review Board. The Principal Investigator (PI) and each of the other health professionals involved in the study (i.e., Mary Schneider, MSN, RN; Susana Crespo, BSN, RN; Kathleen Raviele, MD, a to-be-named research assistant) and the biostatistician Mingan Yang, PhD, will have obtained certification in the conduct of ethical research from the NIH before initiating the study. Volunteer couple data confidentiality, volunteer identification, informed consent, research honesty and HIPAA regulations will also be emphasized during the training sessions for the project research assistant and health professional

involved in the study. The PI and Mary Schneider have attended a number of required HIPAA workshops sponsored by the University and the College of Nursing.

2. Risks to participants. There are no health risks to the participants (male or female) for participating in the study. The risk for the female participant is unintended pregnancy. The participants will be seeking to learn how to use natural means for family planning. Many couples seek this form of family planning because it is non-hormonal – i.e., it has no medical side effects. They will be well informed in an online written form of the possible risks of pregnancy.

3. Human subject protection. Each member of the participating couple will sign an online consent form that describes the study, their involvement, and their right to withdraw from the study at any time. The couple participants will be well aware of the risks of achieving pregnancy by use of a natural method of family planning and will have chosen to use NFP as their preferred method for birth control. All data charts will be kept confidential and will be maintained in a secured online server system. Charts and data forms will be identified by a numbered coding system instead of the subjects' names. The data generated from this study will be presented in oral, poster, or paper format only in aggregate form or with participants' non-identifying variables. The couple volunteers will realize that the intent of the study is in essence to determine the risk of pregnancy in using this form of family planning.

4. Potential benefits for the couple volunteers. All couples will be learning a form of family planning that they are seeking to use in their relationship. They will all receive a $200 electronic fertility monitor and $10 for each menstrual cycle of data that they provide. With the EHFM or with CMM they will be able to monitor the female partner's menstrual cycle, her hormones, and learn about human reproduction. Couples who use natural methods commonly report greater understanding of human reproduction.[68]

5. Importance of the knowledge gained. The results of the study will help determine if the use of an online EHFM or CMM only NFP method with a fertility algorithm are viable methods of

family planning for couples who choose to use a natural method. The results will also assist in deepening our understanding of acceptability, ease of use, and motivation for family planning methods. Acceptability, ease of use, and motivation are key components in the use of and adherence to contraceptive methods. Knowledge of whether the CMM or EHFM is more efficacious will be important for family planning decision making for potential users and providers.

F. Plan for distribution of findings

The findings of this proposed study will be communicated in a number of ways and in a number of venues. First of all, the findings will be written up as a report for the requirements of this proposal, i.e., a 3– 4,000 word lay person report to be submitted to the Office of Population Affairs. A more formal scientific report will be developed and submitted to a peer reviewed scientific journal such as the journal *Contraception* and the *Journal of Obstetric, Gynecology and Neonatal Nursing*. Abstracts of the report will be submitted to regional and national nursing research and family planning conferences (e.g., Midwest Nursing Research Society) for oral or poster presentations. The PI will also offer to present the report and updates on NFP to the Title X Family Planning nurse practitioner providers (through the Region V MPRES Family Planning Training program) and by use of an online Webinar or telephone conference method.

G. Study Timeline.

Duration of study. We estimate that it will take two years to enroll all 750 couples and teach them to use either the CBFM or CMM for avoiding pregnancy. There will be another 12 months until all couples have completed the study. Data analysis, interpretation, and writing the final reports will occur in the final year. Aggregate clinical evaluation of the EHFM and the CMM for avoiding pregnancy will take place when 300 couples in each study group have completed at

least 12 months of use or have attained an unintended pregnancy. It is estimated that it will take about 2 years to collect this data and 3 years to complete the study.

Time	Task	Responsible Person
Modification of NFP Web Site		
1. First 6 months	Contract Web developers for changes	Principle Investigator
	Develop registration Web site	PI & Project Assistants
	Pre-purchase of fertility monitors	PI & Project Assistants
	Advertise online for participants	Project Assistants
Recruitment and Training of Subjects		
2. Year 1 through 3	Continue to advertise for volunteers	PI & Project Assistants
	Enroll couples into study	PI & Project Assistants
	Assess couples consistency in charting	Project Assistants
	Conduct pregnancy evaluations	Project Assistants/PI
	Data entry	Research Assistant
	Begin to analyze data from 1st 100	PI, Bio-statistician
Completion, Analysis, Writing Reports		
3. Final year (Year 3)	Complete final assessments	Project Assistants
	Complete final data collection	Project Assistants
	Complete final pregnancy evals	Project Assistants/PI
	Enter the final data	Research assistant
4. Final 6 months	Analyze and interpret the data	PI/Bio-statistician
	Write report/manuscript for publication	PI/Consultant
	Present reports at professional meetings	PI/Co-PI/Consultant

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