Randomized Trial Comparing Bleeding Patterns after Immediate and Conventional Oral Contraceptive Initiation

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1.0 Summary

Background

In the United Stated, oral contraceptives (OCs) are conventionally initiated during a woman's menstrual period. An alternative approach to OC initiation is the directly-observed, immediate initiation of OCs at the time of clinic visit, regardless of menstrual cycle day. We call this approach "Quickstart". Starting oral contraceptives immediately, under direct observation, increases OC initiation rates and may increase effective use and continuation. However, if adverse bleeding patterns occur, then such an approach may paradoxically decrease continuation rates. The purpose of this study is to compare 90-day bleeding patterns following immediate ("Quickstart") versus conventional OC initiation.

Design

This study was a randomized trial comparing 90-day bleeding patterns between women who started their OCs immediately at the time of study enrollment (Quickstart, intervention) and women assigned to begin their OCs conventionally on the first Sunday after the start of their next menstrual period (Conventional Start, control). The primary outcome was a comparison of the total number of bleeding/spotting days in the 90-day reference period between the two groups. The trial was conducted in the Department of Obstetrics and Gynecology at Columbia-Presbyterian Medical Center in New York from February 2000 to August 2001.

Methods

Eligible women (18-35 years-old; regular menstrual bleeding in the past 12 months; no contraindications to OC use; not current users of hormonal contraception) underwent a routine assessment and pregnancy test at baseline. Each participant received a 4-month supply of a monophasic 35mcg ethinyl estradiol OC and a bleeding diary; was randomized to Quickstart or Conventional Start; underwent monthly follow-up; and, after 90-days, returned the diary and completed an exit interview. Bleeding patterns were assessed using the modified WHO 90-day reference period method. Analysis was performed by trial assignment group (Quickstart versus Conventional Start) and menstrual cycle day of OC initiation (Day 8+ OC Start versus Day 1-7 OC Start).

Results

There was no difference in the number of bleeding/spotting days (adjusted mean difference: -0.39 days; 95% CI: -3.49 to 2.69; p=0.80) or any other outcome between the Quickstart and Conventional Start groups. Furthermore, no differences were observed when the data were analyzed by menstrual cycle day of OC initiation.

Conclusion

Starting oral contraceptives with the Quickstart approach does not induce bleeding patterns which differ from those induced by conventional oral contraceptive starting regimens. Concern about adverse bleeding patterns should no longer be used as a justification for instructing women to wait until their next menses before staring oral contraceptives.

2.0 Introduction

2.1 Unintended pregnancy in the United States

Unintended pregnancy and unplanned birth are common in the United States. Based on data from the 1995 National Surveys of Family Growth (NSFG)[1], excluding miscarriages, 49% of pregnancies in the United States in 1994 were unintended; 54% of these ended in abortion. Forty-eight percent of women aged 15-44 had at least one unplanned pregnancy sometime in their lives; 28% had one or more unplanned births, 30% had one or more abortions; and 11% had both an unplanned birth and an abortion (Henshaw 1998). Overall, about half of U.S. women of reproductive age have had an unintended pregnancy (Forrest 1994). Although the impact of unintended pregnancy on individual women or couples varies, such pregnancies have been linked to social and health problems (Brown and Eisenberg 1995). Almost half of unintended pregnancies occur during a month in which women report using a reversible method of contraception (Forrest 1994).

2.2 Oral contraceptive prevalence in the United States

Oral contraceptives (OCs) are the most popular form of reversible contraception in the United States (Rosenberg and Waugh 1998), comprising approximately 27% of contraceptive use among women age 15-44 using any method of contraception; 52% of contraceptive use among women age 20-24; and 44% of contraceptive use among teenagers in 1995 (Piccinino and Mosher 1998). Oral contraceptives provide high

contraceptive efficacy if used correctly and in typical use[2], as well as many non-contraceptive health benefits such as decreased menstrual cramping, protection against endometrial and ovarian cancers, benign breast disease, ovarian cysts, pelvic inflammatory disease and ectopic pregnancy (Kaunitz 1999; Hatcher, et al. 1994).

2.3 Oral contraceptive acceptors and fertility

Oral contraceptive acceptors (women who present at family planning clinics to obtain oral contraceptives) are typically already sexually active or intend to initiate sexual activity very soon and are, therefore, at high risk of pregnancy. By presenting at a family planning clinic to obtain contraception, these women have demonstrated both that they want avoid becoming pregnant, and that they are motivated to take action to prevent pregnancy. After obtaining a prescription for OCs or receiving the pills themselves at the clinic visit, OC acceptors have the means to prevent pregnancy. Nonetheless, there are high rates of pregnancy among oral contraceptive acceptors in the United States. Rosenberg, et al. (1995b) estimate that approximately one million unintended pregnancies (or 33% of the 3.5 million unintended pregnancies that occur each year in the United States) are due to OC misuse, failure, or inappropriate or premature discontinuation. At twelve months after OC acceptance, reported pregnancy rates in adolescents choosing oral contraceptives range from 19% (Woods, et al. 1992) to 25% (Berenson, et al. 1997a) to 38% (Polaneczky, et al. 1994) to 52% (Emans, et al. 1987). These studies were small and had substantial losses to follow-up, but the high rates of

[1] Nationally representative surveys that collect detailed reproductive and contraceptive histories and related information from women of reproductive age.

pregnancy observed at one year among OC acceptors are supported by nationally representative data from the 1988 and 1995 National Survey of Family Growth (Fu, et al. 1999; Forrest 1994; Jones and Forrest 1992). The 1995 NSFG survey found pregnancy rates in the first year of OC use to be 8% in all OC acceptors and 16% among low income, 20-24 year old acceptors (Fu, et al. 1999).

2.4 Reasons for pregnancy among oral contraceptive acceptors

Unintended pregnancy in the first months after oral contraceptive acceptance occurs for a number of reasons: 1) women become pregnant after the clinic visit and before starting the pill at the next menstrual period; 2) women fail to start the pill at the next menstrual period as instructed; 3) women start the pill, but take it incorrectly; and 4) women discontinue the pill, but remain at risk for unintended pregnancy (early or premature discontinuation). Each of these reasons will be discussed in detail below.

2.4.1 Becoming pregnant after clinic visit and before OC start

Women seeking oral contraception are typically already sexually active or intend to initiate sexual activity very soon, and therefore may be at high risk of pregnancy during the menstrual cycle in which they present at a clinic to obtain oral contraceptives. The conventional approach to initiating oral contraceptives, as prescribed by the United States Food and Drug Administration (FDA) and included in OC package labeling, is to begin by taking the first pill on the first day, first Sunday, or fifth day of the next menses and to use condoms (or another back-up contraceptive method) for the first seven days after OC

[2] Oral contraceptives have 99% efficacy. With typical use, effectiveness is estimated at between 92% and

initiation (Williams-Deane and Potter 1992). Providers routinely instruct women to use abstinence or other methods of contraception until starting the pill and for the first seven days after OC initiation (Speroff and Darney 1996), but by the very act of presenting at a clinic and requesting oral contraceptives, a woman is indicating that alternative approaches to contraception, like the condom or abstinence (which do not require the effort of a clinic visit), may be less acceptable to her at that time.

Furthermore, anecdotal reports from many gynecologists, particularly abortion providers, indicate that many patients report becoming pregnant while waiting to start the pill (Dr. Carolyn Westhoff, personal communication). In randomized trials of hormonal contraceptives, eligible women must wait for their next menses to begin the study medication without using a hormonal method in the interim, and 10-15% of these subjects become pregnant before beginning the study medication (Dr. Carolyn Westhoff, personal communication).

2.4.2 Failure to start OCs at the next menstrual period as instructed

For women who reach their next menses after OC prescription without becoming pregnant, motivation regarding oral contraceptive use may wane by the time of the next menstrual period. Women may forget or become confused about the pill-taking instructions received at the time of OC prescription, and therefore not start at all (Rickert, et al. 1999), or they may receive negative information about OCs from friends or family while waiting and decide they are safer without the OC. In addition, young women may

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97% (Trussel, et al. 1990; Jones and Forrest 1992; Hatcher, et al. 1994).

have an argument with their partner or experience temporary separation and decide that they do not need protection; however, such relationship disturbances are often brief.

In order to minimize or eliminate the effort required to obtain OCs, most family planning clinics provide patients with at least one cycle of pills before leaving the clinic and will provide additional packs at reduced or no cost, so that patients do not have to make a trip to the pharmacy to obtain their OC supplies. However, even in research settings where contraceptive supplies are routinely provided to participants, studies show that from 8% to 24% of adolescents never take the first pill (Polaneczky, et al. 1994; Oakley, et al. 1991). As many as one-half of all women who are no longer using OCs at six months never started the method at all (Berenson, et al. 1997; Berenson and Weimann 1997).

2.4.3 Starting OCs, but taking them incorrectly

Incorrect use of oral contraceptives, as with any oral medication, is widespread and well documented in both adults and adolescents (Cramer 1996). Incorrect use can lead to discontinuation, either due to increased side effects or due to pregnancy (Rosenberg, et al. 1995a; Rosenberg, et al. 1995b).

2.4.4 Early or premature discontinuation of OCs

For women who begin taking pills as instructed, premature discontinuation, meaning discontinuation of oral contraceptives when still at high risk of unintended pregnancy, is prevalent. Multiple studies in a variety of populations show that between 32% and 60% of new oral contraceptive users discontinue the method during the first six months after receiving an initial prescription (Rosenberg and Waugh 1998; Cramer 1996). Berenson,

et al. (1997) showed that only 100 of 189 adolescents (53%) initially prescribed oral contraceptives were still using this method at six months, while Bassalone (1989) reported 50% discontinuation in the first three months of OC use among adolescents. The literature shows high rates of discontinuation at six months, but none of these studies distinguish never-starters from discontinuers. Women who never begin taking their OCs, which may be up to 50% of OC acceptors (Berenson, et al. 1997; Berenson and Wiemann 1997), are a subset of women considered as premature or early discontinuers.

2.5 Reasons for premature OC discontinuation

New users of oral contraception discontinue OC use for many reasons, including fear of side effects, real or perceived side effects, method failure, changes in motivation to prevent pregnancy, and inability to access health services for renewed OC prescriptions or refills (Rosenberg and Waugh 1998; Rosenberg, et al. 1995a; Rosenberg, et al. 1995b; Tyrer 1994).

Side effects are the most frequently reported reason for discontinuing OCs within the first year of use (Rosenberg and Waugh 1998; Rosenberg, et al. 1995a; Hatcher, et al. 1994; Trussel, et al. 1990). Side effects of oral contraceptive initiation include inter-menstrual or irregular bleeding, amenorrhea, nausea, vomiting, edema, breast tenderness, mood changes, headache, and weight changes (Hatcher, et al. 1994). These common minor side effects of OC initiation are typically transient, particularly for those women who are either first time oral contraceptive users or women who have not used oral contraceptives recently (Rosenberg and Waugh 1998; Hatcher, et al. 1994).

Bleeding irregularities in the first few cycles after OC initiation may decrease OC continuation (Hillard 1989). Among the side effects of oral contraceptive initiation, bleeding irregularity is the main reason that women give for discontinuing oral contraceptives when they are still at high risk of unintended pregnancy (Rosenberg and Waugh 1998; Hillard 1989; Emans, et al. 1987). In a recent study of over 1600 women initiating oral contraceptive use or switching to a new OC, Rosenberg and Waugh (1998) found continuation rates at 6 months of 68% among new users and 84% among switchers. Almost one-half (46%) of OC discontinuation was prompted by side-effects, and the most common such side effect reported was bleeding irregularity, which accounted for 12% of overall pill discontinuation in this group of women. It is important to note that this study had a substantial loss to follow-up. However, many studies have found significant proportions of women who offer unacceptable bleeding patterns as a main reason for OC discontinuation (Rosenberg and Long 1992; Hillard 1989; Emans, et al. 1987). There is little data available, however, to compare bleeding patterns between continuing OC users and discontinuers (Belsey 1988a; Neel, et al. 1987). Nevertheless, contraceptive method-induced bleeding irregularity is of concern for both providers and patients, and thus deserves attention when assessing contraceptive innovations (Rosenberg and Waugh 1998; Belsey 1988a; Belsey 1988b).

2.6 Conventional oral contraceptive initiation approaches

The conventional approach to initiating oral contraceptives in a non-user is to instruct her to wait until her next menstrual period after prescription before beginning the pills. The

three options for a conventional start at the next menses are: a first-day of menses start, a first-Sunday of menses start, and a fifth-day of menses start (Williams-Deane and Potter 1992). This conventional OC initiation approach, used since 1960, is prescribed by FDA-approved OC package labeling and is the clinical norm in the United States.

2.6.1 Justifications for conventional start

The main justification for waiting until the next menstrual period to start OCs is that the occurrence of bleeding prior to OC start is meant to indicate that the woman is not pregnant when she starts the pills. When oral contraceptives were first introduced in the 1960's, there was no information about whether or how exposure to contraceptive hormones might affect an embryo or fetus. During the years following oral contraceptive introduction, occurrences of inadvertent exposure during pregnancy were identified, allowing the evaluation of whether the oral contraceptives taken in pregnancy are teratogenic or otherwise dangerous to a pregnancy. A meta-analysis of 12 prospective studies (Bracken 1990) with published results (6,102 exposed pregnancies and 83,167 unexposed pregnancies) provides strong evidence that oral contraceptive exposure in early pregnancy is not associated with an increased risk of malformations[3].

Furthermore, initiating oral contraceptives during the menses is intended to minimize the disruption of the bleeding pattern such that the post-OC initiation bleeding pattern mimics a normal menstrual cycle in an untreated woman and is, therefore, more

[3] Mantel-Haenszel relative risk estimate for all malformations across the 12 studies is 0.99 (95% CI 0.83-1.19). A separate analysis of the risk of congenital heart defects found a relative risk of 1.06 (95% CI 0.72-

acceptable to the user (Williams-Deane and Potter 1992). Using any of the three conventional OC start approaches is intended to lead to a withdrawal bleed at the end of the first cycle of pills, occurring about four weeks after the previous menstrual flow during which OCs were initiated. However, abnormal and breakthrough bleeding is common in the first three to six months of OC use among women initiating low estrogen dose OCs conventionally. Low dose pills (35 mcg estrogen or less) are the predominant OC type currently in use in the United States and worldwide. Higher dose pills (50 mcg estrogen) are typically no longer used because of the greater risk of adverse events associated with higher estrogen doses (Grimes 1992). The estrogen component in combined oral contraceptives is intended to stabilize the endometrium and help provide regular bleeding. However, as the estrogen dose in combined OCs has decreased, irregular and breakthrough bleeding in the early cycles of OC use have increased (Grimes 1992).

After more than three decades of clinical and research experience with oral contraceptives, there is sound evidence that exposure to OCs in pregnancy does not cause birth defects, and that increased irregular bleeding during the first few cycles of OC use is prevalent with low estrogen dose pills, even when conventional starting regimens are followed.

1.56) based on 8 of the studies with sufficiently detailed data. A separate analysis of the risk of limb reduction defects based on 6 studies yielded a relative risk of 1.04 (95% CI 0.30-3.55).

2.7 The Quickstart concept

The conventional initiation of oral contraception described above (i.e., during menses) may mean that a woman waits several weeks after prescription to take the first pill. During this time, up to 25% of OC acceptors do not begin their OCs after receiving a prescription (Polaneczky, et al. 1994). Reasons for non-initiation of OCs at next menstrual period among OC acceptors include: intervening pregnancy between OC prescription and next menstrual period; changes in contraceptive motivation before the next menstrual period (Moore, et al. 1996); confusion about OC starting instructions or forgetting starting instructions altogether (Rickert, et al. 1999); or general fear of initiation because of fear of possible side effects.

An alternative to the conventional approach to OC initiation is to start a woman on oral contraceptives immediately, under direct observation, at the time of her clinic visit seeking OCs, regardless of her menstrual cycle day. We call this immediate, directly observed OC initiation approach "Quickstart". This alternative initiation approach has been employed in the Columbia-Presbyterian Family Planning Clinics (CPMC) in New York City since 1997 and is now the standard of care in these clinics (Dr. Carolyn Westhoff, personal communication). With the Quickstart approach, women seeking OCs swallow their first OC pill under direct observation of the healthcare provider during the clinic visit, regardless of menstrual cycle day, and then continue daily pill use without waiting until the next menses. Pregnancy tests and emergency contraception are used as clinically indicated. To our knowledge, there is no published or unpublished information,

other than our own work, describing or evaluating the use of immediate, directly observed OC initiation approaches (Westhoff, et al. 2001).

2.7.1 Immediate start of OCs in other countries

Regulatory and clinical guidelines in the United States stipulate initiation of OCs within seven days of the start of a woman's menstrual period. However, some international and non-U.S. contraceptive guidelines recommend an "anytime in menstrual cycle" OC start. The World Health Organization Technical Guidance/ Competence Working Group Recommendations for Updating Selected Practices in Contraceptive Use (1994; 1996) recommends that "combined OCs may be started at any time you can be reasonably sure that a woman is not pregnant, for example during the seven days that begin with the onset of menses (days 1 through 7 of the menstrual cycle)". The guidelines suggest the use of a checklist to rule out pregnancy in settings where reliable early pregnancy testing is unavailable. This World Health Organization directive has been incorporated into some national guidelines and has become the standard of care in some countries. For example, the South African contraceptive guidelines state that timing of initiation of hormonal contraceptives should not be restricted to menstruation as this restriction is unnecessary and merely acts as a barrier to access. According to the South African guidelines a woman can start a hormonal method of her choice at any time during her cycle providing she is reasonably sure she is not pregnant. Although anytime OC start is the current policy in South Africa, data is not available to demonstrate how or if this policy is being implemented in clinical settings.

2.7.2 Benefits of the Quickstart approach

Quickstart capitalizes on the high level of contraceptive motivation required for a woman to present at a clinic and request OCs and provides an immediate gratification for the effort and time required in making the clinic visit, as a woman is "on the pill" when she leaves the clinic. For women who have had unprotected sexual intercourse in the 72 hours prior to clinic visit, Quickstart can work in conjunction with emergency contraception (EC), with OC start immediately after the EC regimen is completed. Quickstart results in greater OC initiation, as all women requesting OCs have initiated OC use by the time they leave the clinic[4]. This approach leads to a faster onset of contraceptive protection, as the woman is protected from pregnancy within one week of her clinic presentation.

Furthermore, this approach eliminates the need for the patient to remember the specific starting instructions for a future date (next menses); she can, therefore, focus on remembering other parts of the pill-taking instructions. Thus, Quickstart greatly simplifies the health education associated with OC initiation, both for the provider and the patient.

Finally, Quickstart may lead to higher oral contraceptive continuation rates and, therefore, lower unintended pregnancy rates among OC acceptors. In a prospective observational study of 250 new OC acceptors, Quickstart resulted in greater short-term OC continuation when compared with the conventional starting regimen. After

[4] With the exception of women with a positive pregnancy test, who are referred for appropriate care.

adjustment for all other factors associated with OC discontinuation (age, partner knowledge of OC use and desire for pregnancy in the next six months), women who took their first OC pill under direct observation at the time of their clinic visit and regardless of menstrual cycle day were 2.7 (95% CI for odds ratio: 1.1-6.8) times more likely to continue to their second pack of pills than women who were given conventional starting instructions (Westhoff, et al., 2001) (Appendix 8.10).

Within clinical settings innovative interventions to improve contraceptive compliance are rare for a number of reasons, particularly because of concerns about increasing costs (Armstrong and Stover 1994). The implementation of the Quickstart approach requires brief staff training and no other resources. Therefore, the Quickstart model has the potential to improve contraceptive practice and delivery in the United States and around the world, even in resource-poor health service settings.

2.7.3 Concerns about the Quickstart approach

The Quickstart approach requires no additional human or financial resources, is easy to implement; simplifies health education; increases OC initiation; and may increase effective use and continuation.

However, many clinicians are concerned that Quickstart, which may mean starting OCs outside of the first seven days of the menstrual cycle and outside of FDA-approved OC labeling, may result in appreciably more bleeding irregularity than the conventional start approach. In particular, there is concern that Quickstart will cause more bleeding and

spotting in the first few cycles than conventional OC initiation; that the frequency of bleeding problems after Quickstart will not decrease with continuing OC use, as is observed with conventional starting regimens; and that the cycle control comparable to that achieved by conventional starting regimens will not be achieved within the first few cycles of use after Quickstart. Clinicians are concerned that this simplified approach may paradoxically decrease OC continuation rates, as abnormal or irregular bleeding is regarded as an important side-effect reason for OC discontinuation in both adolescent and adult pill users (Rosenberg and Waugh 1998; Rosenberg and Long 1992).

2.8 Bleeding patterns following low dose oral contraceptive initiation

The disturbance in vaginal bleeding induced by many methods of contraception is an important side-effect because of its potential impact on method acceptability (Belsey and Carlson 1991). Disturbances in bleeding patterns caused by various methods of contraception have been among the main reasons given by women for method discontinuation (Belsey, et al. 1986). Cycle control, namely, predictable bleeding, is an important determinant of whether a new user of OCs will continue the method (Rosenberg and Long 1992). Irregular bleeding patterns after OC initiation are considered to be more common with the use of low dose estrogen pills as opposed to high dose estrogen pills (Speroff and Darney 1996).

Most data on changes in bleeding patterns among new users of OCs come from studies that have been conducted to assess the cycle control provided by oral contraceptives, comparing high- and lower- dose oral contraceptives, and comparing different

formulations of low dose OCs (i.e., different phasing, different progestin components, etc.). A myriad of studies are available on the topic of cycle control after low dose OC initiation (Garceau, et al. 2000; Rosenberg, et al. 1999; DelConte 1999; Archer, et al. 1999; Mircette Study Group 1998; Serfaty and Vree 1998; Endrikat 1997; Akerlund, et al. 1993; Percival-Smith, et al. 1990; Edgren, et al. 1989; Schilling, et al. 1989; Droegemueller, et al. 1989; Appel, et al. 1987). However, comparison of study results across OC formulations is difficult for a number of reasons. Among these reasons are that cycle control as an outcome is subject to intra-study and inter-study variation; and most studies have small sample sizes making it difficult to identify clinically meaningful differences and to measure and control for key factors, such as age, smoking, missed pills or new starters versus switchers, all of which may influence bleeding patterns and skew results (Thorneycroft 1999). Furthermore, the existing literature on post-OC initiation bleeding irregularities uses varying definitions for bleeding problems, varying reference periods for data collection, and varying methods of analysis, rather than the World Health Organization (WHO) recommended 90-day reference period method, and the WHO definitions for clinically important bleeding patterns (Belsey 1988a; Belsey and Farley 1988; Belsey, et al. 1988), which have specific definitions (Belsey, et al. 1997).

Two prospective observational studies (Yeshaya, et al. 1998; Yeshaya, et al. 1996) compared the number of "breakthough bleeding events" (defined as bleeding requiring use of a pad or vaginal tampon during the time active oral contraceptives were taken) during the first cycle of low-dose OC (30 mcg EE) use in subjects initiating OCs on the first day of menses versus subjects initiating OCs on the last day or fifth-day of menses.

These studies observed fewer "breakthough bleeding events" and a shorter mean duration of menses during the first OC cycle in last day/fifth-day starters compared to first-day starters. Although Yeshaya, et al. (1998; 1996) identify and attempt to answer an important question regarding differences in short-term bleeding outcomes between two commonly used conventional OC starting regimens, the studies are methodologically weak. Subjects in these studies are not randomized to treatment groups; the study outcomes are not adjusted for potential confounding variables (i.e., number of missed pills and cigarette smoking); and the unit of analysis for the comparison of "breakthrough bleeding events" is not specified. Furthermore, no information is given regarding the inclusion or exclusion of bleeding events continuous with initial menses. This dearth of information coupled with the above-mentioned methodological weaknesses renders the study results largely uninterpretable. As a result of these methodological shortcomings, these studies, although relevant in their choice of research question, in fact contribute little to the body of literature on cycle control.

Despite the above-mentioned limitations, the oral contraceptive cycle control literature proves useful for purposes of broadly describing the prevalence of bleeding irregularities among new users of low-dose OCs in the first one to three cycles. The incidence of breakthrough or inter-menstrual bleeding/spotting measured in studies of women using a variety of low-dose OC formulations ranges from 10-50%. For example, in a randomized trial of 206 women starting low-dose oral contraceptives, 17%-42% experienced abnormal bleeding and spotting during the first cycle and 8%-29% experienced inter-menstrual bleeding in the second cycle (Droegemueller, et al. 1989). Another randomized

trial of 313 women starting low-dose oral contraceptives found that 20-65% experienced breakthrough bleeding in the first cycle, 20-50% in the second cycle, 25-40% in the third cycle, and 18-45% in the fourth cycle (Schilling, et al. 1989). A study of 321 low dose OC starters and switchers found an incidence of breakthrough bleeding/spotting of 11% in cycle two, which decreased to around 6% for the remainder of the year (Garceau, et al. 2000).

Overall, two conclusions can be drawn from the body of literature on bleeding irregularities in the first few cycles among new users of low-dose oral contraceptives: 1) irregular bleeding is prevalent in pill users during the first few cycles after OC initiation and 2) the frequency of irregular bleeding decreases with continuing OC use.

2.8.1 Women's perceptions of bleeding change after method initiation

A woman's experience of blood loss is very subjective (Belsey and Farley 1988; Snowden and Christian 1983). Experts in the field of fertility regulation suggest that it is the perception of blood loss by a woman, and not necessarily the documented or measurable pattern of bleeding, which is most important in determining her behavior in terms of contraceptive method satisfaction and adherence (Belsey and Farley 1988; Belsey, et al. 1986; Fraser, et al. 1984; Snowden and Christian 1983; Rodriguez, et al. 1976). A woman's pre-existing experience may influence her ability to tolerate bleeding disturbances and perceived changes in her bleeding pattern (Belsey, et al. 1986). Knowledge and understanding of women's perceptions of bleeding changes, in addition

to measurable patterns of bleeding change, are essential for effective counseling, health education and product development (Belsey, et al. 1986).

2.8.2 Bleeding patterns after immediate OC initiation

There is no published or unpublished information describing the pattern of bleeding after oral contraceptive initiation with OC starting regimens other than the conventional start regimen.

2.9 Recording and assessing bleeding patterns

2.9.1 Standardized methods for recording bleeding data

Data on women's bleeding patterns is difficult to standardize since each woman relates to her individual experience of menstruation in a different way (Belsey and Farley 1988; Belsey, et al. 1986). The current standard for collecting data on bleeding patterns in studies of contraceptive methods and bleeding is to record the occurrence of bleeding, which is defined as the loss of blood needing sanitary protection; and spotting, which is defined as the loss of blood without the need for sanitary protection; in a daily diary that is maintained throughout a pre-specified follow-up period. The collection of such data allows the bleeding patterns of individuals to be examined and related to other variables such as the reason given for method discontinuation (Belsey, et al. 1986) or the method of OC initiation. The daily diary method has been shown to be highly reliable and valid (Snowden 1977; Rodriguez, et al. 1976; Treloar 1967).

2.9.2 Approaches to describing and comparing bleeding patterns

Several approaches to the description of vaginal bleeding patterns have been proposed, and evaluations of their suitability have been made by different groups. The two most commonly used approaches in bleeding pattern analysis are the reference period analysis method and the cycle-based analysis method.

The reference period analysis method was recommended in 1986 by WHO Special Program of Research Development and Research Training in Human Reproduction (Belsey, et al. 1986). It is based on the reference period method originally developed by Rodriguez et al. (1976). Using the reference period method, data from menstrual diaries are analyzed on the basis of reference periods (RP), usually 90-days long (Belsey, et al. 1986), and the woman is the unit of analysis. The WHO Reference Period Method, which stipulates a minimum reference period of 90-days, originally recommended that the following bleeding pattern indices be calculated for each reference period covered by the woman's bleeding diary: a) number of bleeding/spotting days; b) number of spotting days; c) number of bleeding/spotting episodes; d) number of spotting-only episodes; e) mean, range and maximum value of lengths of bleeding/spotting episodes; and f) mean, range and maximum value of lengths of bleeding-free intervals. However, it was later determined that most of the essential information about a woman's bleeding pattern is contained in only four of the 10 recommended indices: 1) number of bleeding/spotting episodes; 2) the mean lengths of bleeding/spotting episodes; 3) the mean lengths of bleeding-free intervals; and 4) the range of bleeding-free intervals (Belsey and Carlson 1991). Together, these indices describe the most important dimensions of a bleeding

pattern: the amount, frequency and predictability of the bleeding (Belsey and Carlson 1991).

Using these standardized indices, episodes of bleeding and spotting can then be tallied over intervals of 90 days from the daily menstrual diaries, and patterns can then be compared among subgroups or among different hormonal contraceptives in a uniform fashion. Standardized definitions of bleeding and spotting have been developed by WHO and clinically significant bleeding patterns (including amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding, and prolonged bleeding) have also been identified by WHO and have specific definitions (Belsey, et al. 1997). The occurrence of each of these clinically significant patterns can be determined from a review of the diary.

The WHO Reference Period Method has provided researchers in the field of fertility regulation with methods of data collection that are reliable, applicable in different cultural settings, usable by illiterate women, able to capture vastly different menstrual disturbances (from prolonged amenorrhoea, to episodes of light bleeding or spotting occurring every few days, to 'normal' patterns) and easy to analyze (Belsey and Carlson 1991). Because this method is based on a specified reference period, instead of cycles, it allows for comparison of bleeding patterns across contraceptive methods that cycle differently. One drawback of 90-day reference period-based analysis is that it may be difficult for clinicians to interpret and present in an understandable way to patients initiating method use.

Another approach to the analysis of vaginal bleeding patterns is to use the menstrual cycle as the unit for analysis. Women think in terms of cycles, and clinicians need to be able to translate bleeding patterns identified in research into cycle terms for counseling purposes. Thus, a more clinically meaningful method of bleeding pattern analysis may be a cycle-based approach. However the length of the menstrual cycle varies both within and between women (Treloar, et al. 1967), and use of a cycle-based approach requires identification and definition of what constitutes inter-menstrual bleeding. For this reason the cycle is not generally recommended as an appropriate unit for analysis. The only exception, according to Belsey, et al. (1986), is the particular case of oral contraceptives as the method itself imposes a fixed 28-day time-frame designed to regulate menstrual bleeding. Thus, cycle-based analysis may be useful in certain circumstances to measure the departure of the observed bleeding pattern from the expected one. Cycle-based analysis is relevant and useful when comparing methods that have comparable cycles, in other words, which are standardized by design (i.e., when comparing two 28-day pill regimens or when comparing a 28-day pill regimens with a monthly injectable with 28-day administration intervals). However, definitions, event inclusion/exclusion criteria, and the specific analytic methods used in cycle-based analyses need to be standardized in order to minimize *post hoc* data manipulation (Thorneycroft 1999).

2.10 Study purpose

Quickstart simplifies health education, increases OC initiation and may increase OC effective use and continuation. However, if adverse bleeding patterns occur with the Quickstart approach in comparison to the Conventional Start approach, then this simplified approach may paradoxically decrease OC continuation rates. The purpose of this study is to compare 90-day bleeding patterns in women randomized to Quickstart and conventional OC initiation to determine if bleeding patterns following Quickstart are meaningfully and appreciably different from bleeding patterns following the conventional start of OCs.

2.10.1 Primary outcome

The primary outcome of this study is the comparison of the mean number of bleeding and spotting days in the 90-day reference period in the Quickstart and Conventional Start groups.

2.10.2 Secondary outcomes

The study has a number of secondary outcomes:

1) A comparison of the number of women in the two groups discontinuing oral contraceptives in the 90-day follow-up period;
2) A comparison of the WHO-defined bleeding, spotting and no-flow indices in the two groups;
3) A comparison of the proportion of women in the two groups experiencing WHO-defined clinically important bleeding patterns in the 90-day follow-up period;

4) A comparison of perceptions of bleeding change after OC initiation in the two groups;

5) A comparison of OC method satisfaction and OC continuation in the two groups.

3.0 Methods

This study was conducted as a randomized controlled trial in the Department of Obstetrics and Gynecology at Columbia-Presbyterian Medical Center in New York City between February 2000 and August 2001. Eligible women were randomly assigned to one of two oral contraceptive (OC) initiation regimens: Quickstart (intervention group) or Conventional Start (control group). Quickstart is defined as the immediate start of OCs (including the directly observed ingestion of the first pill) at the time of study enrollment, regardless of a woman's menstrual cycle day. Conventional Start is defined as the initiation of OCs on the first Sunday of a woman's next menstrual period after study enrollment. The conventional starting regimen is prescribed by FDA-approved OC package labeling and is the clinical norm.

3.1 Participant recruitment and eligibility

Women were recruited for participation via advertisements at Columbia University and advertisements in the local newspapers. Two screenings were used to determine study eligibility. Interested women were first screened by telephone (Appendix 8.2) and scheduled for a second in-person screening if they met the following inclusion criteria: English or Spanish-speaking; 18-35 years of age; regular menstrual bleeding (12 cycles of 21-35 days) in the past 12 months; no contraindications to OC use; no current use of hormonal contraception (>2 menses since last use for OCs, injectables, Norplant or IUD);

not recently pregnant (>1 menses beyond post-abortion bleed for first trimester TOP[5]; >2 menses beyond post-abortion bleed for second trimester TOP; >2 menses post-partum); and not recent users of emergency contraception (>1 menses beyond post-EC bleed).

At the in-person screening, women underwent a routine clinical assessment (history and blood pressure), a urine pregnancy test, and were interviewed regarding sexual activity in the 10 days prior to the in-person screening visit (Appendix 8.3). Women with either a positive urine pregnancy test or any episode of unprotected sex in the 10 days prior to the screening visit were considered ineligible, as were women with any previously undetected contraindications to the use of OCs. Women who tested positive for pregnancy were referred for appropriate care. Women who reported unprotected sexual intercourse in the previous 72 hours were offered emergency contraception.

3.2 Participant enrollment and baseline assessment

Eligible women signed the study consent form (Appendix 8.4) and an oral contraceptive consent form (Appendix 8.5), as is protocol in the CPMC Family Planning Clinics. They were then administered a baseline questionnaire by a trained interviewer to collect demographic information, menstrual bleeding and symptoms, contraceptive and reproductive history, fertility motivation, and partner influence around contraceptive use (Appendix 8.6). Participants received a 4-month supply of a monophasic 35mcg ethinyl estradiol (EE) oral contraceptive, 10 condoms, and a bleeding diary with standardized definitions of bleeding, spotting and no menstrual flow (Appendix 8.8).

[5] TOP = termination of pregnancy

At the end of the enrollment visit, each participant was randomized to either Quickstart (intervention) or Conventional Start of OCs. After assignment, women were counseled on consistent condom use prior to OC initiation and for the first seven days of pill use, correct pill-taking procedures, and what to do in the event of missed pills or discontinuation. Women assigned to immediate OC start (Quickstart) ingested the first pill under observation of the researcher at the end of the enrollment visit. Women assigned to conventional start were instructed to take the first pill on the first Sunday of their next menstrual period. Participants recorded the occurrence of bleeding, spotting or no menstrual flow in their bleeding diary everyday for 90 days from the day of first pill.

3.3 Randomization

Participants were assigned to either the intervention (Quickstart) or control (Conventional Start) group with 60% and 40% probability, respectively. Random assignments were generated two months prior to the start of participant recruitment by a statistician not involved in the study, using a random numbers table. Assignments were concealed in sequentially numbered, signed and sealed opaque envelopes until the moment of participant assignment at the conclusion of the enrollment visit.

3.4 Follow-up procedures and exit assessment

Each participant was followed-up monthly by telephone to assess OC continuation and for the collection of bleeding diary entries (bleeding, spotting or no flow for each calendar day from OC initiation). After 90-days from first pill, participants returned their

bleeding diary and completed an in-person exit interview regarding OC continuation, symptoms and perceptions of post-OC initiation bleeding (Appendix 8.7). For the purposes of the study, bleeding is defined as bloody vaginal discharge requiring sanitary protection with a tampon or maxi-pad; spotting is defined as bloody vaginal discharge requiring the use of a "panty-liner" or no sanitary protection; and no-flow is defined as the absence of bleeding or spotting.

3.5 Sample size and power

The required sample size was calculated for our primary outcome, the total number of bleeding and spotting days (hereafter, bleeding/spotting) in the 90-day reference period. Based on the work of Belsey, et al. (1997), we expected an average of 19 bleeding/spotting days and a standard deviation of 6 bleeding/spotting days in a 90-day reference period. We postulated that both OC starting regimens would produce an equivalent number of bleeding/spotting days in a 90-day reference period, and defined clinically-meaningful equivalence as a difference of less than 5 bleeding/spotting days between the two groups. The study was designed to have 95% power to detect this clinically important difference in bleeding/spotting days. Using a significance level of 0.05, a ratio of intervention to control of 1.0, and a two-sided test, a total of approximately 80 women (40 Quickstart and 40 Conventional Start) were required for the study.

We planned *a priori* to analyze the data by menstrual cycle day of OC initiation (referred to here as the start-day analysis) in addition to trial assignment (referred to here as the

intention-to-treat analysis). In anticipation of the start-day analysis, we planned to recruit at least 100 participants for randomization to Quickstart and Conventional Start in a ratio of 1.5 to 1.0 (giving us at least 60 Quickstart subjects and 40 Conventional Start subjects). Women presented for their enrollment visits throughout their menstrual cycles. The typical menstrual cycle is about four weeks long. Therefore, we anticipated that approximately one-quarter of women would be enrolled during days one through seven of their menstrual cycle. Therefore, on average, one-quarter of the women randomized to Quickstart would begin their OCs during days 1-7 of their menstrual cycle, which could be regarded as a conventional start (according to FDA-approved OC labeling). Randomizing at least 100 participants to Quickstart or Conventional Start in this ratio (60% probability of being assigned to Quickstart and 40% probability of being assigned to Conventional Start) ensured that we would have at least 40 subjects who started their OCs outside of menstrual cycle day 1-7.

3.6 Ethics

The study was approved by the Institutional Review Board of Columbia University (Appendix 8.9). Women were paid $140.00 as compensation for their participation in the study. The study drug was provided by the Ortho-McNeil Pharmaceutical Corporation.

3.7 Description of study drug

All participants (both intervention and control) received a four-month supply of Ortho-Novum ® 1/35, an FDA-approved oral contraceptive which is widely prescribed in the United States. This is a combined monophasic oral contraceptive (each pill has an

estrogen and a progestin) with 28 tablets per cycle (21 hormonally active tablets followed by 7 placebo tablets), and a formulation of 1mg norethindrone and 35mcg ethinyl estradiol (EE).

3.8 Data analysis

Bleeding diary entries were abstracted and entered into SPSS 9.0 for analysis (SPSS Corporation, Chicago, USA) by a researcher external to the study and blinded to trial assignment. Baseline and follow-up variables were examined using descriptive summary statistics in order to describe the two groups and to identify imbalances between the two groups, as well as to identify any potential confounding variables.

3.8.1 WHO reference period analysis method

The WHO reference period (RP) analysis method, which uses the woman as the unit of analysis (Belsey, et al. 1988; Rodriguez, et al. 1976), was employed. The length of the reference period for the WHO reference period analysis is 90-days. The reference period started on the day that the first pill was taken (day of enrollment visit for women assigned to Quickstart or first Sunday of menstrual period after enrollment visit for women assigned to Conventional Start) and ended 90 days from OC initiation. For each woman, the following menstrual indices were calculated from the diary for the 90-day reference period:

1) number of bleeding/spotting days;
2) number of bleeding/spotting episodes (any set of one or more bleeding/spotting days bounded at each end by two or more bleeding/spotting-free days);

3) mean length of bleeding/spotting episodes;
4) mean length of bleeding/spotting-free intervals (any set of two or more consecutive bleeding-free days bounded at each end by bleeding or spotting days);
5) range of bleeding-free interval lengths.

Indices were calculated only if the woman had complete diary data (that is consecutively for 90-days in a 90-day period). The event (i.e., bleeding/spotting day, bleeding/spotting episode or bleeding-free interval) in progress when recording commenced was excluded from all calculations[6], as was any event censored by termination of the diary.

Each index was then summarized over the subjects in each OC initiation group. The means and mean differences with 95% confidence intervals, and 25th, 50th and 75th percentiles were calculated. The student's *t*-test was used to compare means and the Mann-Whitney *U* test was used to compare medians (50th percentiles). Although these indices were typically normally distributed, both means and medians are presented to allow comparison with previously published data. Mean differences were adjusted for confounding variables, where necessary, using multiple linear regression. All mean differences are calculated as intervention minus control (i.e., Quickstart minus Conventional Start, or Day 8+ OC Start minus Day 1-7 OC Start). The type of bleeding subjects experienced in the 90-day reference period was characterized into clinically

[6] Exclusion of the event in progress at the commencement of the diary (i.e., OC initiation) is recommended by WHO. This exclusion is of particular relevance to this study as by definition many more subjects in the Conventional Start group are bleeding at the time of OC initiation than subjects in the Quickstart group.

important bleeding sub-groups and compared using a Pearson's chi-square test. All comparisons were two-sided, with p-values of less than 0.1 considered significant.

3.8.2 Intention-to-treat and start-day analyses

As was described in the sample size and power section, subjects presented for their enrollment visits throughout their menstrual cycles. The typical menstrual cycle is about four weeks long, so it was anticipated that approximately one-quarter of women would be enrolled in the study during days 1-7 of their menstrual cycle. Therefore one-quarter of the women randomized to Quickstart would begin their OCs during days 1-7 of their menstrual cycle, which could be regarded as a conventional start. To account for this we conducted all analyses two ways: a) by trial assignment (referred to here as the intention-to-treat analysis) and b) by menstrual cycle day of OC initiation (referred to here as the start-day analysis). In the start-day analysis, menstrual cycle day of OC initiation was defined as the number of days from the start of the last menstrual period. Starting between day 1 and day 7 is consistent with FDA-approved labeling for OC initiation and a day 8+ start is an off-label initiation regimen.

3.8.3 Note on data available for analysis

At the time of writing of this dissertation, 9 of the 113 subjects enrolled in this trial (6 Quickstart and 3 Conventional Start) have yet to complete the 90-day study follow-up period. All of these subjects have already completed over 60 days of follow-up and have had two telephonic follow-up contacts with the researchers. All of these subjects are on schedule and will complete the study by September 16, 2001; none have been lost to

follow-up. Due to the deadline for submission of this dissertation, all analyses presented here are based on the 104 subjects who have completed the study as of August 10, 2001 (95 subjects who have successfully completed the 90-day follow-up as of August 10, 2001 and 9 subjects who have discontinued OCs or lost to follow-up as of August 10, 2001). Baseline enrollment data is presented for the entire sample of enrolled subjects (113). Outcome data is presented for only those 95 subjects who have successfully completed the 90-day study follow-up period as of August 10, 2001.

4.0 Results

The flow of participants through the trial is shown in Figure 1. A total of 113 healthy women were recruited and randomized to begin their oral contraceptives (OCs) either by Quickstart (59%, n=67) or Conventional Start (41%, n=46) (Table 1a). All 46 of the subjects randomized to Conventional Start took the first pill during day 1-7 of the menstrual cycle. Of the 67 subjects randomized to Quickstart, 13 (19%) ingesting their first pill under direct observation at the end of their enrollment visit (i.e., Quickstart by trial assignment) started OCs during day 1-7 of their menstrual cycle (see Table 1b). According to FDA-approved oral contraceptive labeling, these 13 subjects technically followed a conventional starting regimen by taking the first OC pill within the first seven days of their menstrual cycle.

In total, 59 subjects (52%) started OCs during day 1-7 of the menstrual cycle, while 54 (48%) started OCs during day 8 or after of the menstrual cycle (start outside of FDA-approved OC labeling) (Table 1b). As planned *a priori*, the data are analyzed both by trial assignment (intention-to-treat analysis: Quickstart vs. Conventional Start) and by menstrual cycle day of OC initiation (start-day analysis: Day 8+ OC Start vs. Day 1-7 OC Start).

The number of subjects in each trial assignment group starting OCs on cycle day 1-7, cycle day 8-14, and cycle day 15+ is shown in Table 1c.

4.1 Participant follow-up

To date, 95 participants have successfully completed the study's follow-up period of 90 days from the day of OC initiation: 57 Quickstart (85%) and 38 Conventional Start (83%), or 45 Day 8+ OC Start (83%) and 50 Day 1-7 OC Start (85%).

4.2 Description of subjects lost to follow-up

Nine subjects (4 Quickstart and 5 Conventional Start) exited the study prematurely. Table 2 provides the reasons and time of exit from the study for the nine subjects who were not followed for the full 90-day period. Of the four women in the Quickstart group who did not complete the study, one discontinued OCs because of acne (exited after 31 days of follow-up); one because of mood changes (29 days); one because of pregnancy (28 days); and one woman was ruled ineligible after randomization and exited from the study immediately (0 days).

Of the five women in the Conventional Start group who did not complete the study, one discontinued OCs because of nausea (61 days); one because of mood changes (30 days); one on a doctor's recommendation because of a breast lump (68 days); one because of an intervening pregnancy between study enrolment and pill start (0 days); and one woman was lost to follow-up for unknown reasons (0 days).

The four women in the Quickstart group who did not complete the study started their OCs on day 8+ of their menstrual cycle (all Day 8+ OC Start). By design, the five women

in the Conventional Start group who did not complete the study started their OCs on day 1-7 of their menstrual cycle (all Day 1-7 OC Start). There were no significant differences in baseline characteristics between the participants who did not complete the study follow-up period and those who did (data not shown).

4.3 Oral contraceptive discontinuation

There was no significant difference in OC continuation rates between the Quickstart and Conventional Start groups (p=0.48), and no subjects discontinued OCs for a bleeding-related reason.

4.4 Analysis by trial assignment (intention-to-treat analysis)

4.4.1 Baseline participant characteristics

There were few differences in baseline characteristics between the two randomized assignment groups. Parity was higher in the Quickstart group (Table 3a). Twenty-two percent (15) of the women randomized to Quickstart had had at least one birth, compared with 6.5% (3) of the women randomized to Conventional Start. This difference in proportions was statistically significant (p=0.04). Although the proportion of current smokers was the same in the two groups (17.9% and 17.4%), the median number of cigarettes smoked per day was slightly higher in the Quickstart group compared to the Conventional Start group, though this difference was not statistically significant (3.0 vs. 1.5; p=0.2).

4.4.2 Identification of potential confounding variables

On average, randomization of subjects tends to produce balance in both measured and unknown risk factors between trial assignment groups; however, this does not guarantee balance of all characteristics in a single experiment. As described above, there was a chance imbalance in parity between the Quickstart and Conventional Start groups in our trial. Parity was found to be significantly associated with our primary outcome, total number of bleeding/spotting days (Tables 12a, 12b and 12c). As a result, we adjusted our primary outcome, total number of bleeding/spotting days, and all of the other menstrual indices for parity (as a binary variable, ever/never given birth) using multiple linear regression. Parity was found to be a weak positive confounder of the association between trial assignment and bleeding/spotting; however, adjustment for parity did not change any inferences regarding the outcomes of the study.

There was no statistically significant difference in consistency of OC use in the 90-day follow-up period between the Quickstart and Conventional Start groups (Table 4a). However, consistency of OC use was found to be associated with the primary outcome, total number of bleeding/spotting days (Tables 11a, 11b and 11c), and there is evidence to suggest that missed pills and inconsistent pill use are associated with increased bleeding and spotting among women using OCs (Thorneycroft 1999; Rosenberg, et al. 1996a; Rosenberg, et al. 1995c). Therefore, we evaluated this potential confounder by including it as a covariate in the multiple linear regression model which also contained trial assignment (Quickstart vs. Conventional Start) and parity. Adjustment for

consistency of OC use did not change any inferences regarding the outcomes of the study.

4.4.3 Overall results

Our results show no difference between the Quickstart and Conventional Start groups in our primary outcome, total number of bleeding/spotting days, as well as all of the WHO-defined menstrual indices. Figure 2 shows the percentage of subjects experiencing bleeding or spotting on each day of the 90-day follow-up period in the Quickstart and Conventional Start groups.

4.4.4 Number of bleeding and spotting days

Table 5a shows the means for the total number of bleeding/spotting days for the trial assignment groups (the primary outcome), with mean differences and 95% confidence intervals. The mean number of bleeding/spotting days in the 90-day reference period was similar between Quickstart (18.95 days) and Conventional Start (19.50 days) (mean difference, Quickstart - Conventional Start = -0.55 days; 95% CI: -3.60 to 2.49; p=0.72). The difference in means represents slightly fewer bleeding/spotting days in the Quickstart group as compared with the Conventional Start group. Even after adjustment for parity and number of pills missed, there was no difference between the two treatment groups in the total number of bleeding/spotting days (adjusted mean difference = -0.39 days; 95% CI: -3.49 to 2.69; p=0.80). The median number of bleeding/spotting days was also similar in the two groups (17.0 days for Quickstart and 18.0 days for Conventional Start; p=0.89) (Table 6a).

The mean number of spotting days in the 90-day reference period was similar in Quickstart (8.63 days) and Conventional Start (9.39 days) (Table 5a). The mean difference was -0.76 days (95% CI: -3.23 to 1.70; p=0.54), representing slightly fewer spotting days in the Quickstart group as compared with the Conventional Start group. This insignificant difference remained after adjustment for parity and number of pills missed (adjusted mean difference = -0.56 days; 95% CI: -3.13 to 2.00; p=0.67). The median number of spotting days was the same in the two groups (7.0 days) (Table 6a).

The mean number of bleeding days in the 90-day reference period was similar in the Quickstart and Conventional Start groups (10.32 days and 10.11 days, respectively; mean difference = 0.21 days; 95% CI:-1.97 to 2.39; p=0.85) (Table 5a). After adjustment for parity and number of pills missed, there was still no difference in total number of bleeding days in the two groups (adjusted mean difference = 0.16 days; 95% CI: -2.05 to 2.38; p=0.88). The median number of bleeding days was similar in the two groups (10.0 days in the Quickstart group and 9.0 days in the Conventional Start group; p=0.78) (Table 6a).

4.4.5 Number of bleeding and spotting episodes

The mean number of bleeding/spotting episodes in the 90-day reference period was 3.68 episodes in the Quickstart group and 3.95 episodes in the Conventional Start group. The mean difference was -0.26 episodes (95% CI: -0.76 to 0.24; p=0.30) (Table 5a). This insignificant difference in the number of bleeding/spotting episodes remained after

adjustment for the parity and number of pills missed (adjusted mean difference = -0.26 episodes; 95% CI: -0.76 to 0.24; p=0.30). The median number of bleeding/spotting episodes was 3.0 in the Quickstart group and 4.0 in the Conventional Start group (p=0.45) (Table 6a).

4.4.6 Length of bleeding and spotting episodes

The mean length of bleeding/spotting episodes was 5.28 days in the Quickstart group and 5.22 days in the Conventional Start group (mean difference= 0.06 days; 95% CI: -0.67 to 0.79; p=0.87) (Table 5a). Even after adjustment for parity and number of missed pills, there was no difference in the mean length of bleeding/spotting episodes in the two groups (adjusted mean difference = 0.09 days; 95% CI: -0.64 to 0.83; p=0.79). The median length of bleeding/spotting episodes was similar in the two groups (5.25 days in the Quickstart group and 4.75 days in the Conventional Start group; p=0.71) (Table 6a).

4.4.7 Length of bleeding and spotting-free intervals

The mean length of bleeding/spotting-free intervals was 17.74 days in the Quickstart group and 16.93 days in the Conventional Start group (mean difference = 0.81 days; 95% CI: -1.82 to 3.45; p=0.54), representing slightly longer bleeding/spotting-free intervals in the Quickstart group (Table 5a). After adjustment for parity and number of pills missed, there was no difference in the length of the bleeding/spotting-free intervals in the two groups (adjusted mean difference = 0.37 days; 95% CI: -2.23 to 2.96; p=0.78). The median length of bleeding/spotting-free intervals was 18.50 days in the Quickstart group and 17.17 days in the Conventional Start group (p=0.60) (Table 6a).

The mean range of the bleeding/spotting-free interval lengths was 9.91 days in the Quickstart group compared with 12.84 days in the Conventional Start group (mean difference= -2.93 days; 95% CI: -6.18 to 0.32; p=0.10), representing a smaller range of bleeding/spotting-free intervals in the Quickstart group (Table 5a). After adjustment for parity and number of pills missed, there was no difference in the range of bleeding/spotting-free interval lengths in the two groups (adjusted mean difference = -3.16 days; 95% CI: -6.46 to 0.45; p=0.10). The median range of bleeding/spotting-free interval lengths was 10.0 days in the Quickstart group and 13.5 days in the Conventional Start group (p=0.10) (Table 6a).

4.5 Analysis by menstrual cycle day of OC initiation (start-day analysis)

4.5.1 Baseline participant characteristics

When the participant's baseline characteristics were analyzed according to menstrual cycle day of OC initiation (Table 3b), they were also similar for the two groups. Parity was balanced in the Day 8+ OC Start group and the Day 1-7 OC start group (18.5% vs. 13.6%; p=0.61). However, there were some differences. A greater proportion of women in the Day 1-7 OC Start group were current smokers (22.0% vs. 13.0%), but this difference in proportions was not statistically significant (p=0.2). Among current smokers, there was a statistically significant difference in the median number of cigarettes smoked per day (p=0.02), with women in the Day 8+ OC Start group smoking

4.0 cigarettes per day and women in the Day 1-7 OC Start group smoking 1.0 cigarette per day.

4.5.2 Identification of potential confounding variables

Subjects were not randomly assigned to Day 8+ OC Start and Day 1-7 OC Start for the start-day analysis. While parity was balanced in this analysis, there was a statistically significant difference in the number of cigarettes smoked per day in the two groups. Smoking (both as a continuous variable, number of cigarettes per day and as a binary variable, current smoking status) was not statistically significantly associated with our primary outcome, total number of bleeding/spotting days (Tables 13a , 13b and 13c). However, cigarette smoking has been shown to be associated with a number of antiestrogenic effects (Baron and Greenberg 1987), and there is some evidence to suggest that smoking may also adversely effect cycle control with oral contraceptives (Thorneycroft 1999; Rosenberg, et al. 1996b; Rosenberg, et al. 1995c). As a result, we adjusted our primary outcome, total number of bleeding/spotting days, and all of the other menstrual indices for smoking (as a continuous variable, number of cigarettes smoked per day) using multiple linear regression. Number of cigarettes smoked per day was determined not to be a confounder in the association between menstrual cycle day of OC start and bleeding/spotting. Adjustment for number of cigarettes smoked per day did not change our inferences about the outcomes of the study.

There was not a statistically significant difference in consistency of OC use in the 90-day follow-up period between the Day 8+ OC Start and Day 1-7 OC Start groups (Table 4b).

However, consistency of OC use was found to be associated with the primary outcome, total number of bleeding/spotting days (Tables 11a, 11d and 11e). Because missed pills and inconsistent pill use are associated with increased bleeding and spotting among women using OCs (Thorneycroft 1999; Rosenberg, et al. 1996a), we evaluated consistency of OC use as a potential confounder by including it as a covariate in a multiple linear regression model which also contained menstrual cycle day of OC initiation (Day 8+ OC Start vs. Day 1-7 OC Start) and number of cigarettes smoked per day. Adjustment for consistency of OC use did not change our inferences about the outcomes of the study.

4.5.3 Overall results

Results similar to those of the intention-to-treat analysis were observed for all outcomes when the data were analyzed according to menstrual cycle day of OC initiation (start-day analysis). Figure 3 shows the percentage of subjects experiencing bleeding or spotting on each day of the 90-day follow-up period in the Day 8+ OC Start and Day 1-7 OC Start groups.

4.5.4 Number of bleeding and spotting days

Slightly more bleeding/spotting days were observed in women starting OCs on Day 8+ as compared to women starting on Day 1-7 (Table 5b). The mean number of bleeding/spotting days in the 90-day reference period was not significantly different between the Day 8+ OC Start (20.16 days) and the Day 1-7 OC Start (18.28 days) groups. The mean difference was 1.88 days (95% CI: -1.04 to 4.84; p=0.21). After adjustment for

smoking and number of pills missed, there was still no significant difference in total bleeding/spotting days in the two groups (adjusted mean difference = 1.49 days; 95% CI: -1.60 to 4.58; p=0.34). The median number of bleeding/spotting days was not significantly different in the two groups (18.0 days in Day 8+ OC Start vs. 16.0 days in Day 1-7 OC Start; p=0.12).

Slightly more spotting days were observed in women starting on Day 8+ (9.16 days) as compared to women starting on Day 1-7 (8.74 days). The mean difference was 0.42 days (95% CI: -2.01 to 2.84; p=0.73) (Table 5b). After adjustment for smoking and number of pills missed, there was no significant difference in total spotting days in the two groups (adjusted mean difference =0.43 days; 95% CI: -2.14 to 2.98; p=0.74). The median number of spotting days was not significantly different in the two groups (8.0 days in Day 8+ OC Start vs. 7.0 days in Day 1-7 OC Start; p=0.64) (Table 6b).

The mean number of bleeding days in the 90-day reference period was not significantly different between the Day 8+ OC Start (11.00 days) and Day 1-7 OC Start (9.54 days) groups (Table 5b). The mean difference was 1.46 days (95% CI: -0.65 to 3.57; p=0.20) representing slightly fewer bleeding days in the Day 1-7 starters as compared with the Day 8+ starters. After adjustment for smoking and number of pills missed, there was no significant difference in total bleeding days in the two groups (adjusted mean difference =1.06 days; 95% CI: -1.12 to 3.25; p=0.34). The median number of bleeding days was not significantly different in the two groups (11.0 days in Day 8+ OC Start vs. 9.0 days in Day 1-7 OC Start; p=0.18) (Table 6b).

4.5.5 Number of bleeding and spotting episodes

The mean number of bleeding/spotting episodes in the 90-day reference period was 3.78 episodes in the Day 8+ OC Start group and 3.80 episodes in the Day 1-7 OC Start group (Table 5b). The mean difference was -0.02 episodes (95% CI: -0.52 to 0.47; p=0.93), representing the same number of bleeding/spotting episodes in the two groups. After adjustment for smoking and number of pills missed, there was still no significant difference in number of bleeding/spotting episodes in the two groups (adjusted mean difference = -0.12 episodes; 95% CI: -0.62 to 0.38; p=0.63). The median number of bleeding/spotting episodes was 4.0 in the Day 8+ OC Start group and 3.0 in the Day 1-7 OC Start group (p=0.80) (Table 6b).

4.5.6 Length of bleeding and spotting episodes

In the start-day analysis, the mean length of bleeding/spotting episodes was 5.42 days in the Day 8+ OC Start group and 5.11 days in the Day 1-7 Start group (Table 5b). The mean difference was 0.31 days (95% CI: -0.40 to 1.02; p=0.40). After adjustment for smoking and number of pills missed, there was no significant difference in the length of bleeding/spotting episodes in the two groups (adjusted mean difference = 0.31 days; 95% CI: -0.41 to 1.03; p=0.40). The median length of bleeding/spotting episodes was 5.6 days in the Day 8+ OC Start group and 4.6 days in the Day 1-7 OC Start group (p=0.16) (Table 6b).

4.5.7 Length of bleeding and spotting-free intervals

The mean length of bleeding/spotting-free intervals was 17.14 days in the Day 8+ OC Start group and 17.66 days in the Day OC 1-7 Start group (Table 5b). The mean difference was -0.52 days (95% CI: -3.11 to 2.08; p=0.69). After adjustment for smoking and number of pills missed, there was no significant difference in the length of bleeding/spotting-free intervals in the two groups (adjusted mean difference = -0.31 days; 95% CI: -2.97 to 2.36; p=0.82). The median length of bleeding/spotting-free intervals was 18.16 days in the Day 8+ OC Start group and 17.83 days in the Day 1-7 OC Start group (p=0.86) (Table 6b).

The mean range of the bleeding/spotting-free interval lengths was 10.38 days in the Day 8+ OC Start group and 11.72 days in the Day 1-7 OC Start group (Table 5b). The mean difference was -1.34 days (95% CI: -4.57 to 1.89; p=0.41). After adjustment for smoking and number of pills missed, there was no significant difference in mean range of the bleeding/spotting-free interval lengths in the two groups (adjusted mean difference = -1.73 days; 95% CI:-5.02 to 1.57; p=0.30). The median range of the bleeding/spotting-free interval lengths was the same in both groups (11.0 days) (Table 6b).

4.6 Analysis of clinically important bleeding patterns

The number and percentage of women in each trial assignment group experiencing clinically important bleeding patterns as defined by WHO in the 90-day reference period is shown in Table 7a. Based on the modified WHO definitions, 53% of those beginning by Quickstart and 58% of those beginning by Conventional Start experienced an altered

bleeding pattern in the 90-day reference period. The difference in the proportions of altered bleeding in the two groups was not significant (p=0.77). The most common bleeding disturbances in both groups were irregular bleeding, frequent bleeding and prolonged bleeding. A greater proportion of subjects beginning by Conventional Start experienced irregular, frequent and prolonged bleeding compared to those beginning by Quickstart; however, these differences were not significant (p=0.48, p=0.40 and p=0.96, respectively).

The same results were observed when the data were analyzed according to menstrual cycle day of OC initiation (Table 7b), with a slightly greater proportion of women in the Day 1-7 OC Start group experiencing an altered bleeding pattern than women in the Day 8+ OC Start group (56% vs. 53%; p=0.96). The same proportion of women in both groups experienced prolonged bleeding (p=1.0). Slightly more women in the Day 1-7 OC Start group experienced frequent bleeding (26% vs. 20%; p=0.65) and irregular bleeding (30% vs. 22%; p=0.53) and than women in the Day 8+ OC Start group. None of these differences in proportions were statistically significant.

4.7 Perceptions of bleeding change

Table 8a shows subjects' perceptions of change in their bleeding in the 90 days after oral contraceptive initiation compared with their bleeding in the three months prior to OC initiation. Overall perceptions of bleeding change were not appreciably different in the Quickstart and Conventional Start groups. Similar results were observed when the data were analyzed by menstrual cycle day of OC initiation (Table 8b).

4.8 Overall satisfaction with oral contraceptives

Table 9a presents subjects' satisfaction with the OC method and desire to continue the OC method after the completion of the study. The proportions of women who were satisfied with the OCs; who would make the same decision to start OCs again given their 90-day experience; and who were continuing to use the pill after study completion were the same in the Quickstart and Conventional Start groups. The same results were observed when the data were analyzed by menstrual cycle day of OC initiation (Table 9b).

5.0 Discussion

5.1 Key findings

This is the first study of any design to assess bleeding patterns after immediate oral contraceptive initiation (i.e., OC start on any day of the menstrual cycle). This study directly compares the bleeding patterns induced by an immediate oral contraceptive starting regimen with bleeding patterns induced by a conventional starting regimen (i.e., starting OCs during the first seven days of the menstrual cycle).

Our trial showed that there is no difference in the bleeding patterns induced by immediate and conventional OC starting regimens in the first 90-days after method initiation. We observed equivalence in our primary outcome, the total number of bleeding/spotting days experienced in the first 90-days of OC use in the two groups. Women randomized to Quickstart experienced 18.95 bleeding/spotting days in the 90-day period compared to the 19.50 bleeding/spotting days experienced in the Conventional Start group (adjusted mean difference: -0.39 days; 95% CI: -3.49 to 2.69). We defined a clinically significant difference in bleeding/spotting days *a priori* as a difference of less than five bleeding/spotting days between the groups in the 90-day follow-up period. As indicated by the point estimate (-0.39) and the upper bound of the 95% confidence interval for the mean difference (2.69), our data suggest that Quickstart most likely results in no more bleeding/spotting than Conventional Start. At the most, these data are consistent with Quickstart resulting in approximately three additional bleeding/spotting days in a 90-day period, an estimate well within our definition of clinical equivalence.

In addition to the finding of no difference in our primary outcome, we also found no difference between Quickstart and Conventional Start for each of the other WHO-defined menstrual indices. In other words, we found no difference between Quickstart and Conventional Start in the most important dimensions of a bleeding pattern: the amount, frequency and predictability of the bleeding (Belsey and Carlson 1991). Furthermore, there was no appreciable difference in the proportion of women experiencing altered bleeding patterns, or any of the WHO-defined clinically important bleeding patterns, between the two groups. Perceptions of bleeding change in the 90-day period after OC initiation, as well as method satisfaction and continuation, were very similar in the two groups.

Finally, no differences in bleeding patterns were observed when the data were analyzed by trial assignment (intention-to-treat analysis) or menstrual cycle day of OC initiation (start-day analysis).

5.2 Findings in light of existing literature

There are no published data on bleeding patterns after OC initiation with immediate starting regimens similar to the Quickstart approach used herein. The different definitions of and analytic approaches to bleeding patterns in the literature make it difficult to compare our results to previous studies, which mainly rely on analysis by cycle.

Our primary analysis utilized the reference period method, but we also looked at our data by 28-day pill cycle to determine if the per-cycle bleeding/spotting in our control group (Conventional Start) was consistent with per-cycle bleeding reported in the published literature. Our conventional start group experienced a total of about 8 bleeding/spotting days in the first pill cycle and 5 bleeding/spotting days in the second and third pill cycles (Table 10)[7].

Women starting OCs (i.e., women who have not used OCs for the previous three months), such as those participating in our study, tend to experience more bleeding and spotting in the first one to three pill cycles, both in terms of length of withdrawal bleed and the occurrence of inter-menstrual bleeding/spotting, than later cycles (Garceau, et al. 2000; Rosenberg, et al. 1999; Droegemueller 1989). Irregular bleeding is prevalent in the first cycles after OC initiation; decreases in subsequent pill cycles; and then levels off at approximately 4-5 bleeding/spotting days per OC cycle. Thus, data from our control group (Conventional Start) are consistent with the published cycle-based literature on bleeding and spotting in the first few cycles after low-dose OC initiation.

We have found only one analysis of bleeding patterns after oral contraceptive initiation which uses the 90-day reference period analysis method. This analysis was from a WHO task force (Task Force on Long-Acting Systemic Agents for Fertility Regulation, Development and Research Training in Human Reproduction), which convened to

[7] This analysis excluded bleeding/spotting continuous with the previous menses and did not distinguish between inter-menstrual bleeding/spotting and withdrawal bleeding/spotting.

develop and promote standardized menstrual bleeding measures and analyses. This analysis of 1003 menstrual diaries from clinical trials of three combined oral contraceptives found an average of 12-14 bleeding/spotting days; 3 bleeding/spotting episodes with mean lengths of 4 days; and bleeding-free intervals of 23-24 days per 90-days of OC method use (Belsey 1988b). Our control subjects had about 19 bleeding/spotting days; 4 bleeding/spotting episodes with a length of about 5 days; and bleeding-free intervals of about 17 days. Two of the three OC formulations investigated in the studies analyzed by the WHO task force were of high-estrogen dose (50 mcg of EE), and "new OC users" and "switch-over users" were not distinguished in the presentation of the analysis. Both of these reasons would help to explain the fewer average number of bleeding/spotting days, the fewer episodes, the shorter episode lengths, and longer bleeding-free intervals observed among OC initiators in the WHO analysis compared to our control group.

5.3 Strengths of the study

Our study has several strengths. First, we used the reference period method of analysis, which, although relatively uncommon in the oral contraceptive bleeding literature, offers a number of important advantages. The reference period method specifies time units of follow-up of a standardized length (90 days) and uses standardized, reliable definitions of outcomes (bleeding, spotting and no-flow) and menstrual indices. In addition, the method provides detailed instructions for calculating these indices and clearly defined criteria for the exclusion or inclusion of menstrual events in progress at the start and end of each

reference period. The reference period approach also uses a well-tested and reliable method of data collection.

Overall, the reference period analysis method ensures that outcome measures and methods of analysis are standardized and specified before the start of the study, thus decreasing the opportunity for *post-hoc* manipulation of data which may plague cycle-based analyses of bleeding patterns. Furthermore, use of this method enables the standardized comparison of post-OC initiation bleeding patterns across OC formulations, as well the comparison of post-OC initiation bleeding patterns with the bleeding patterns induced by other long-acting methods of contraception. The review of the OC bleeding patterns literature indicates that standardized approaches to the assessment and presentation of these data are needed.

A second strength of this study is its design, as the randomized controlled trial has several major advantages over other epidemiologic designs (Friedman, et al. 1998; Byar, et al. 1976). Successful randomization removes the possibility of selection bias in the allocation of participants to intervention assignment. Without randomization such bias could easily occur, either consciously or subconsciously on the part of the investigator or participant, and could not necessarily be controlled. Selection bias can influence study results towards or away from the null value and can invalidate the comparison between intervention groups.

Another advantage of randomization is that it tends to produce comparable groups. That is, on average, randomization results in the balance of both measured and unknown risk factors between trial assignment groups. This does not guarantee balance of all baseline characteristics in a single experiment, however. In our trial there was a chance imbalance in parity, but we had sufficient data to adjust for the variable statistically. Overall, a randomized design helps to assure the validity of statistical tests used in analysis and is considered the "gold-standard" of study designs.

A third strength of the study is the prospective collection of outcome data. The reference period method stipulates the prospective recording of menstrual events by participants in a daily calendar record. Events are recorded as they occur, so recall bias, a considerable problem in the study of bleeding patterns because of the recurrent nature of menstrual bleeding (Belsey and Farley 1988; Snowden 1977), is eliminated.

A fourth strength of the study is that the abstraction of the participants' menstrual diary data in preparation for data entry was conducted by a researcher external to the study. This researcher was blinded to participant trial assignment status and to trial outcome, thus eliminating the possibility of assessment bias in the abstraction of diary data.

Finally, very few subjects were lost to follow-up, loss to follow-up was balanced between trial assignment groups, and there were no meaningful baseline differences between subjects who completed the study and those who did not. As a result of our high follow-up rate, we had very high statistical power (greater that 95%) to rule out a clinically

meaningful difference of five or more bleeding/spotting days, our primary outcome, between the groups in both the intention-to-treat and start-day analyses.

5.4 Limitations of the study

This study has a number of potential limitations as well. Subjects and investigators were not blinded to subject's trial assignment. Although blinding, and double-blinding in particular, is ideal for preventing bias during data collection and assessment, not all trials can be conducted in this manner. Given the nature of our intervention (immediate ingestion of the first pill at the time of enrollment visit versus instructions for pill start at next menses) blindness was not possible on a practical level. The blinding of subjects would have been logistically complex and costly; moreover, there is no reason to believe that a subject's knowledge of whether she started the pill immediately or conventionally would have altered her recording of daily menstrual events. All subjects completed the diary for 90-days from the day of pill start, whether pill start was the day of study enrollment or first Sunday of next menses.

Another limitation of the study is that outcome events (daily bleeding, spotting and no-flow) were self-recorded by the participant, rather than biologically measured. However, the prospective, self-recorded calendar method of menstrual data collection has been shown to be reliable and valid for the collection of menstrual bleeding data (Belsey, et al. 1988; Snowden 1977; Rodriguez, et al. 1976; Treloar 1967). Furthermore, because our subjects were contacted by telephone for the collection of their calendar entries several times during the follow-up period in an unscheduled manner, we are confident that we

avoided one of the major problems with diary data: subjects completing all of the daily diaries immediately before the follow-up visit (Steiner, et al. 2001).

Given our finding of no difference in 90-day bleeding patterns between the groups, one concern may be that the observed null finding is the result of non-differential misclassification of bleeding/spotting days by trial subjects. If substantial, this random measurement error could operate to dilute a possible difference in bleeding/spotting days between Quickstart and Conventional Start, thereby creating an observed null association. Although possible in theory, there is considerable evidence to suggest that the measures used here are reliable and valid enough to detect differences in bleeding/spotting. Along these lines, numerous other studies using this method of data collection (the prospective self-recording of menstrual events in a daily diary) have shown marked differences in menstrual bleeding patterns comparing different methods of hormonal contraception (Garceau, et al. 2000; Rosenberg, et al. 1999; DelConte 1999; Zheng, et al. 1999; Affandi 1998; Suvisaari and Lahteenmaki 1996; Fraser 1994; Droegemueller, et al. 1989) and new users versus switch-over users (Edgren, et al. 1989).

Another possible limitation of the study is the generalizability of the findings, given the eligibility criteria for entry and the use of only one OC formulation. Generalizability is often considered a limitation of clinical trial data. The specific eligibility criteria for this study that could make our subjects somewhat different from the general population of OC acceptors are as follows: women included in our study were 18-35 years of age; had regular menstrual bleeding; were not current users of hormonal contraception (>2 menses

since last use); were not recently pregnant (>1 menses beyond post-abortion bleed for first trimester TOP; >2 menses beyond post-abortion bleed for second trimester TOP; >2 menses post-partum); and were not recent users of emergency contraception (>1 menses beyond post-EC bleed). These inclusion/exclusion criteria ensured that the subjects in our study had broadly regular/normal, and similar, bleeding patterns prior to OC initiation, thus minimizing the intrinsic variability among subjects and giving us the best chance (most power) of detecting a difference in bleeding patterns between Quickstart and Conventional Start if there was a true difference.

It is plausible, and in some cases documented, that the underlying bleeding patterns of women included in our study differ from the bleeding patterns of women who were excluded. Bleeding patterns and frequency are different in women of different ages (Belsey, et al. 1997), but women aged 18-35 do represent the vast majority of OC acceptors in the United States. Women switching from one OC to another experience less bleeding irregularity than new users, and women who have recently had an abortion or given birth have altered bleeding patterns compared to women who have not. It is plausible that immediate OC starting regimens could have differential impact on bleeding patterns of women with underlying bleeding patterns different from those included in our study.

OC formulations other than a monophasic 35 mcg EE will result in different bleeding and spotting patterns. For example, women starting lowest-dose OCs (i.e., 20 mcg pills) experience more bleeding/spotting than women starting 30-35 mcg EE pills (Archer, et

al. 1999; Rosenberg, et al. 1999; Rosenberg and Waugh 1998; Grimes 1992). Requiring all subjects to use the same OC was necessary in the study in order to minimize intrinsic variability among study participants, again giving us the best chance (most power) to detect a difference between Quickstart and Conventional Start if there was a true difference. The OC used in this study was chosen because pills of similar estrogen dose comprise about 75% of all OCs currently prescribed in the United States (Contraception Report 1999).

5.5 Research and policy recommendations

This is the first study comparing post-OC initiation bleeding patterns between immediate and conventional OC starting regimens. Because of the randomized design; the reliable method of data collection; the standardized analytic approach; the successful follow-up of participants; and the robustness of the results across all bleeding pattern indices and both planned analyses (i.e., the intention-to-treat and start-day analysis), these results provide strong evidence that the Quickstart approach to OC initiation does not induce bleeding patterns different from those induced by conventional oral contraceptive starting regimens. As a result, concern about adverse bleeding patterns should no longer be used a justification for instructing women to wait until their next menses before starting oral contraceptives.

Because family planning service providers, and nurses in particular, will have primary responsibility for the implementation of Quickstart interventions in most clinical settings, nurse training is a crucial for the success of this useful intervention. From the CPMC

Family Planning Clinic experience, the provider re-training necessary for implementation of the Quickstart approach, while critical to the intervention's success, is minimal and easily incorporated into staff in-service training and continuing education programs. The Quickstart approach requires minimal staff training and no other resources. It is therefore a suitable innovation for all family planning health care services, even services in resource-poor settings.

This randomized trial has shown that starting oral contraceptives with the Quickstart approach does not induce bleeding patterns different from those induced by conventional oral contraceptive starting regimens. A prospective observational study of Quickstart and conventional OC starting regimens has demonstrated that Quickstart leads to increased short-term OC continuation (Westhoff, et al., unpublished data). A key limitation of that observational study is that subjects were not randomly assigned to the OC starting regimen.

To further evaluate the usefulness of Quickstart, a multi-center randomized trial comparing six month OC continuation rates and pregnancy rates among 2000 oral contraceptive acceptors, randomized to either Quickstart or conventional start, is being planned. If Quickstart is found to be only equal to conventional start in terms of long-term OC continuation and pregnancy outcomes in the multi-center trial, the Quickstart approach still has an important role to play in the improvement of contraceptive practice and delivery. Quickstart increases OC initiation rates by design, leads to a faster onset of

contraceptive protection, and greatly simplifies oral contraceptive health education for both providers and patients.

6.0 Figures and Tables

Figure 1.

Flow of participants through each stage of the trial comparing Quickstart and conventional OC starting regimens (as of August 10, 2001).

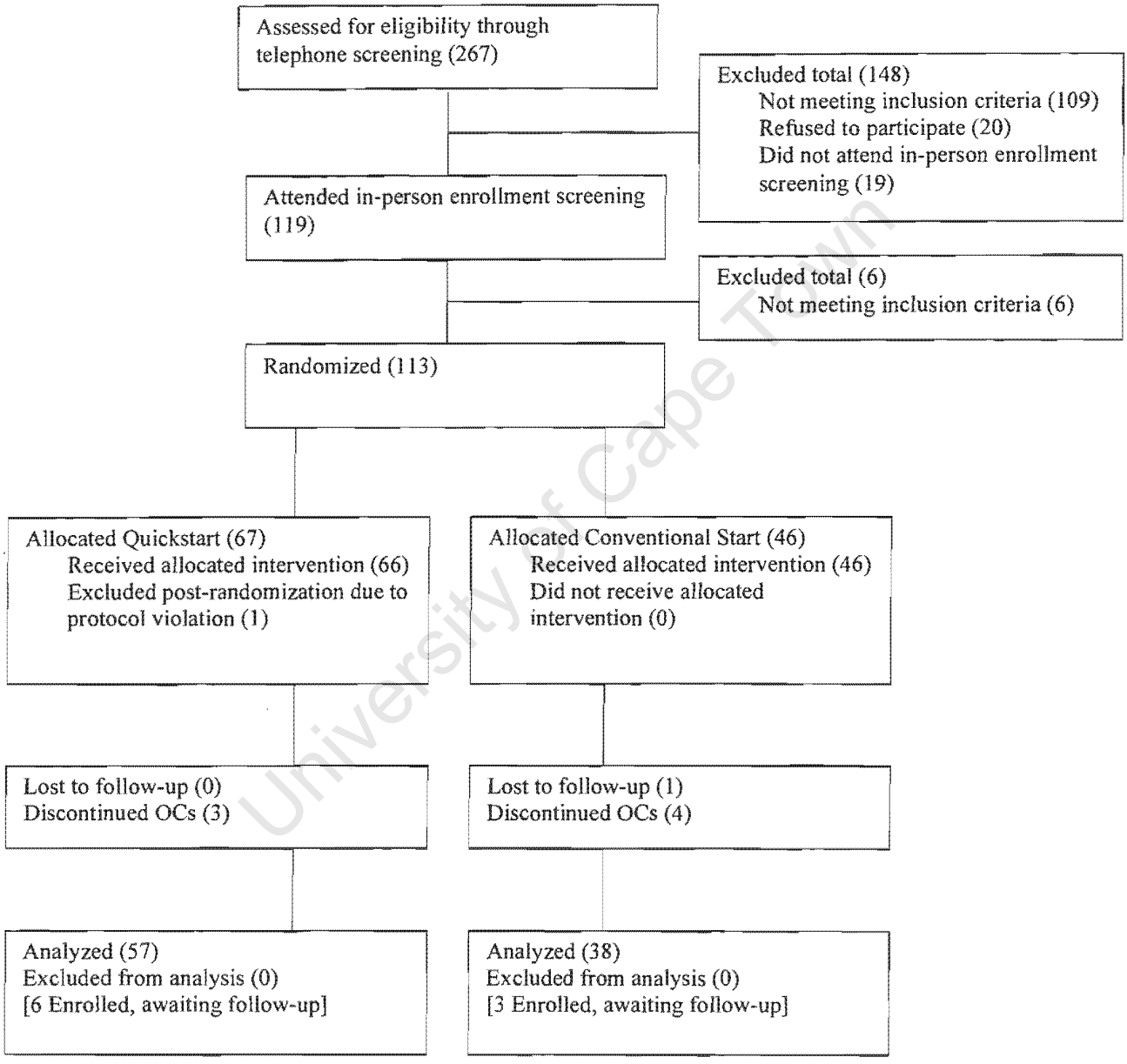

Figure 2. Percentage of Subjects Experiencing Bleeding/Spotting on Each Day of the Follow-up Period by Trial Assignment (Day 1=Day of OC initiation)

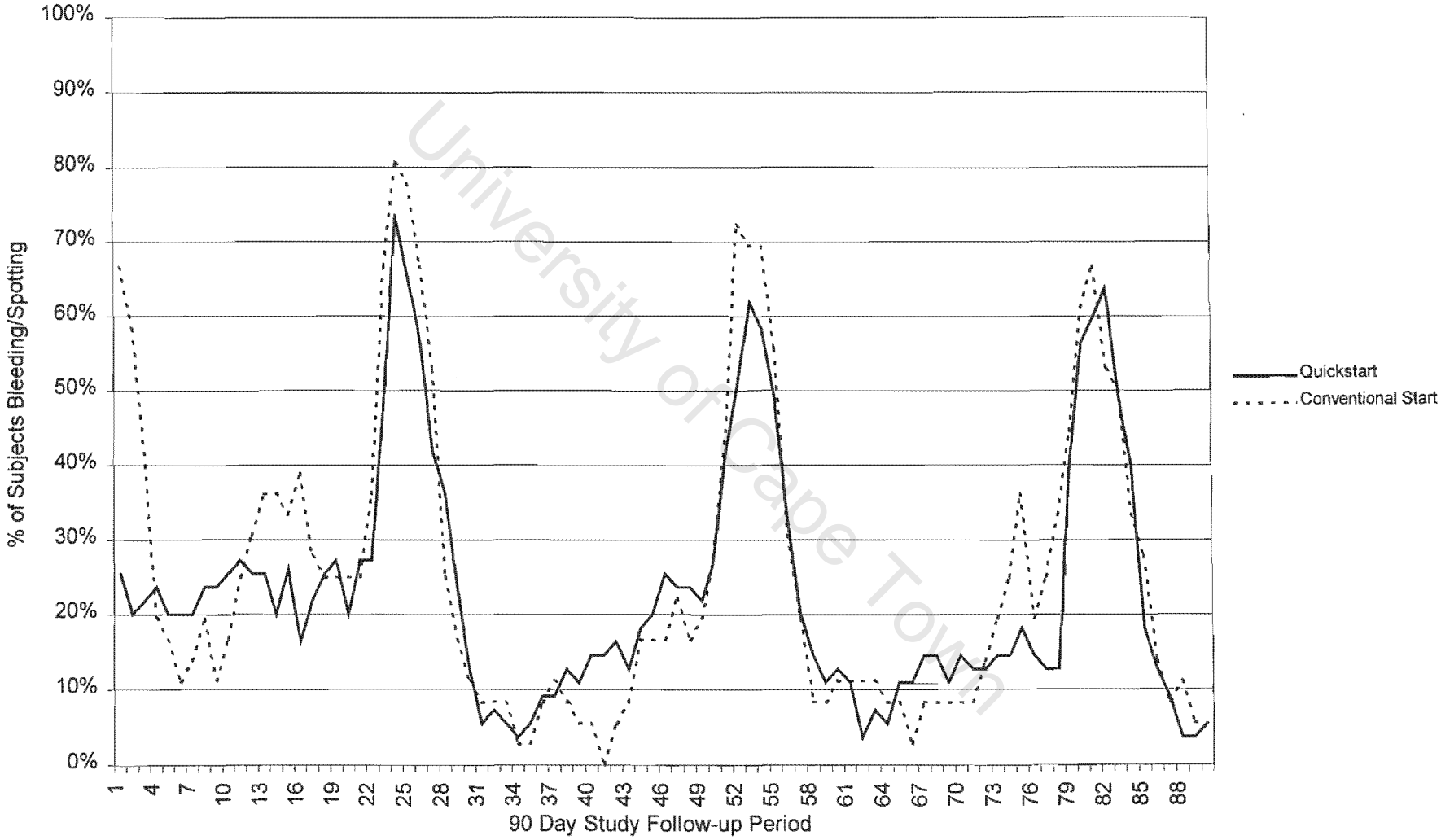

Figure 3. Percentage of Subjects Experiencing Bleeding/Spotting on Each Day of the Follow-up Period by Menstrual Cycle Day of OC Initiation (Day 1=Day of OC Initiation)

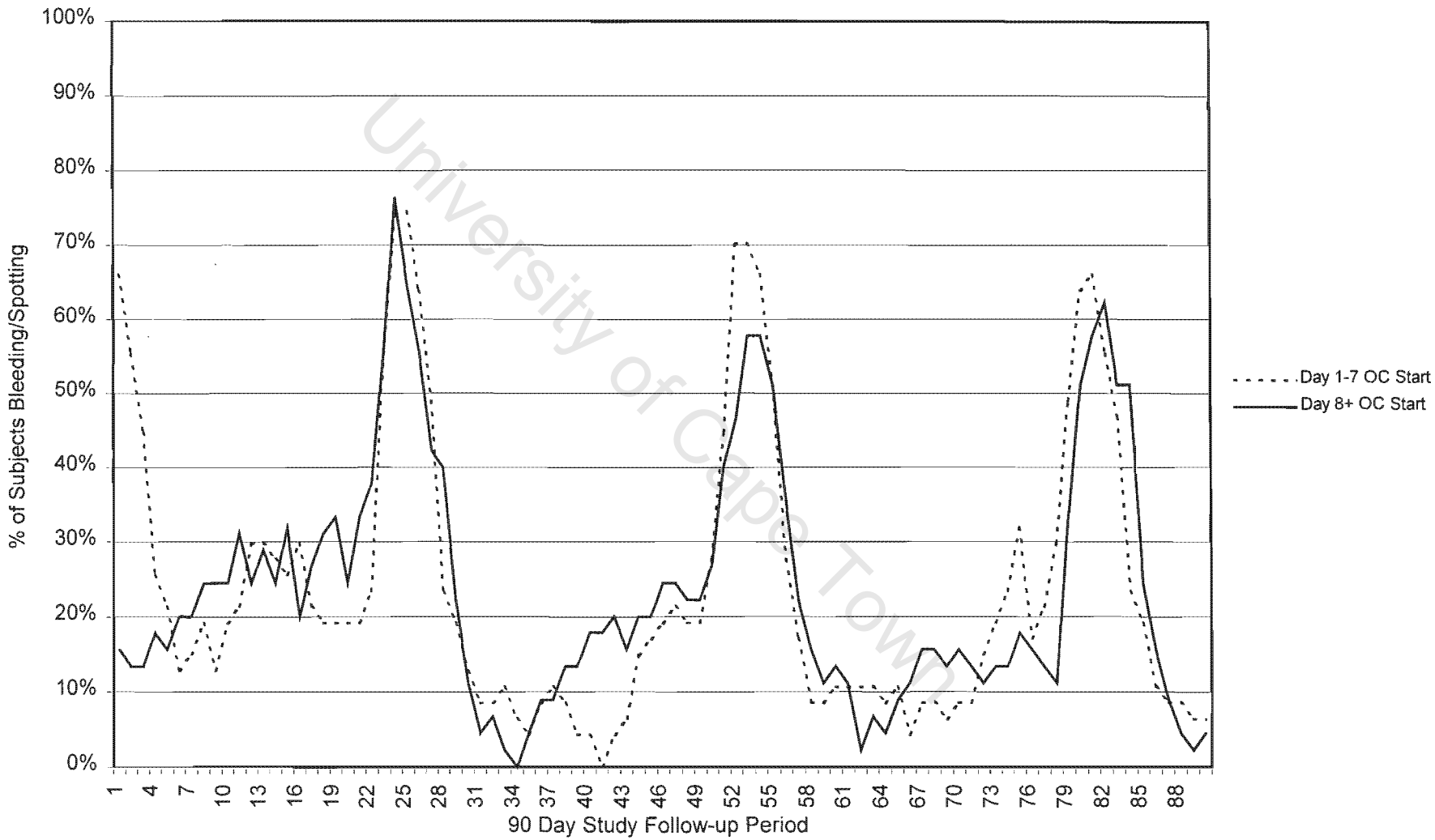

Table 1a.

Number of women recruited and randomized to begin oral contraceptives either by Quickstart or Conventional Start, and number of women starting OCs on menstrual cycle Day 1-7 or menstrual cycle Day 8+ .

Quickstart n(%)	*Conventional Start n(%)*	*Total n(%)*
67 (59)	46 (41)	113 (100)

Day 8+ Start n(%)	*Day 1-7 Start n(%)*	*Total n(%)*
59 (52)	54 (48)	113 (100)

Table 1b.

Number of women randomized to Quickstart and Conventional Start who ingested the first pill during menstrual cycle Day 1-7 and menstrual cycle Day 8+.

	Quickstart n(%)	*Conventional Start n(%)*	*Total n (%)*
Cycle Day 1-7	13 (19.4)	46 (100)	59 (52)
Cycle Day 8+	54 (80.6)	0 (0)	54 (48)
Total	67 (100)	46 (100)	113 (100)

Table 1c.

Number of women randomized to Quickstart and Conventional Start who ingested the first pill during menstrual cycle Day 1-7, menstrual cycle Day 8-14 and menstrual cycle Day 15+.

	Quickstart n(%)	*Conventional Start n(%)*	*Total n(%)*
Cycle Day 1-7	13 (19.4)	46 (100)	59 (52.2)
Cycle Day 8-14	17 (25.4)	0 (0)	17 (15.1)
Cycle Day 15+	37 (55.2)	0 (0)	37 (32.7)
Total	67 (100)	46 (100)	113 (100)

Table 2.

Description of participants randomized to Quickstart and Conventional Start of OCs but not completing 90-day follow-up period (as of August 10, 2001).

Patient	*Assignment*	*Menstrual Cycle Day of OC Initiation*	*Reason for exclusion from analysis*	*Days of follow-up completed*	*Excluded from all analyses*
414	QS*	Day 8+***	Discontinued OCs, acne	31	Yes
418	CS**	Day 1-7****	Lost to follow-up	0	Yes
419	QS	Day 8+	Ruled ineligible after randomization because of protocol violation (menstrual cycle variation of 14-21 days in past 12 months at baseline)	0	Yes
421	CS	Day 1-7	Discontinued OCs, changes in mood	30	Yes
438	CS	Day 1-7	Discontinued OCs, doctor's advice because of breast lump	68	Yes
452	CS	Day 1-7	Did not initiate OCs, pregnancy. Patient became pregnant between enrollment in study and pill start at next menses	0	Yes
471	CS	Day 1-7	Discontinued OCs, nausea	61	Yes
495	QS	Day 8+	Discontinued OCs, pregnancy. Patient had a negative urine pregnancy test and reported no intercourse in 10 days prior to enrolment	28	Yes
510	QS	Day 8+	Discontinued OCs, changes in mood	29	Yes

* QS=Quickstart, ** CS=Conventional Start, ***Day 8+ = menstrual cycle Day 8+ OC Start,**** Day 1-7=menstrual cycle Day 1-7 OC Start.

Table 3a.

Baseline characteristics of women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE oral contraceptive.

	Quickstart *n=67*	*Conventional Start* *n=46*
Age; years		
Mean (standard deviation)	25.4 (4.5)	23.4 (3.8)
Min-max	18-37	18-33
Ethnicity, %		
Hispanic	15.2	15.2
Black	24.2	23.9
White	39.4	39.1
Asian	13.6	15.2
Other	7.6	6.5
Height; inches		
Mean (standard deviation)	64.6 (3.1)	64.8 (3.0)
Weight; lbs.		
Median	131.0	130.0
Smoking		
current smokers, %	17.9	17.4
cigarettes/day, median	3.0	1.5
Prior OC Use		
ever used OCs, %	58.2	52.2
used OCs in last year*, %	40.0	41.7
Difference between maximum and minimum cycle lengths in 12 months prior to study enrollment; days		
Median	3.0	3.0
Intermenstrual bleeding in last year**, %	11.9	13.0
Parity***		
Nulliparous, %	77.6	93.5
Parous, %	22.4	6.5

* All women eligible for participation had >2 menses since last use of OCs
** Spotting or bleeding not continuous with menstrual spotting/bleeding
*** All women eligible for participation in the study had >2 menses post-partum

Table 3b.

Baseline characteristics of women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

	Day 8+ OC Start *n=54*	*Day 1-7 OC Start* *n=59*
Age; years		
Mean (standard deviation)	25.37 (4.2)	23.9 (4.4)
Min-max	18-37	18-35
Ethnicity, %		
Hispanic	14.8	15.3
Black	24.1	25.4
White	38.9	39.0
Asian	13.0	15.3
Other	9.3	5.1
Height; inches		
Mean (standard deviation)	64.6 (3.2)	64.8 (2.9)
Weight; lbs.		
Median	130.0	135.0
Smoking		
current smokers, %	13.0	22.0
cigarettes/day, median	4.0	1.0
Prior OC Use		
ever used OCs, %	57.4	54.2
used OCs in last year*, %	37.8	43.8
Difference between maximum and minimum cycle lengths in 12 months prior to study enrollment; days		
Median	4.0	3.0
Intermenstrual bleeding in last year**, %	13.0	11.9
Parity***		
Nulliparous, %	81.5	86.4
Parous, %	18.5	13.6

* All women eligible for participation had >2 menses since last use of OCs
** Spotting or bleeding not continuous with menstrual spotting/bleeding
*** All women eligible for participation in the study had >2 menses post-partum

Table 4a.

Consistency of OC use in the 90-day follow-up period among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE oral contraceptive.

	Quickstart *n=57*	*Conventional Start* *n=38*	*P-value**
Number of subjects who forgot to take one pill 0, 1, 2, 3, 4 and 5 times during the 90-day follow-up period, n (%)			
0	14 (24.6)	8 (21.0)	
1	15 (26.3)	12 (31.6)	0.76
2	15 (26.3)	12 (31.6)	
3	9 (15.8)	3 (7.9)	
4	3 (5.3)	3 (7.9)	
5	1 (1.7)	0 (0)	
Number of subjects who forgot to take two consecutive pills 0, 1 and 2 times during the 90-day follow-up period, n (%)			
0	49 (86.0)	33 (86.8)	0.85
1	6 (10.5)	3 (7.9)	
2	2 (3.5)	2 (5.3)	
Number of subjects who forgot three consecutive pills and started a new pill pack, n	1	1	1.0
Ever missed a pill, n (%)			
Yes	43 (75.4)	30 (78.9)	0.88
No	14 (24.6)	8 (21.1)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 4b.

Consistency of OC use in the 90-day follow-up period among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

	Day 8+ OC Start n=45	*Day 1-7 OC Start n=50*	*P-value**
Number of subjects who forgot to take one pill 0, 1, 2, 3, 4 and 5 times during the 90-day follow-up period, n (%)			
0	10 (22.2)	12 (24.0)	0.53
1	10 (22.2)	17 (34.0)	
2	13 (28.9)	14 (28.0)	
3	8 (17.8)	4 8.0)	
4	3 (6.7)	3 (6.0)	
5	1 (2.2)	0 (0)	
Number of subjects who forgot to take two consecutive pills 0, 1 and 2 times during the 90-day follow-up period, n (%)			
0	38 (84.5)	44 (88.0)	0.87
1	5 (11.1)	4 (8.0)	
2	2 (4.4)	2 (4.0)	
Number of subjects who forgot three consecutive pills and started a new pill pack, n	1	1	1.0
Ever missed a pill, n (%)			
Yes	35 (77.8)	38 (76.0)	1.0
No	10 (22.2)	12 (24.0)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 5a.

Mean, mean difference and 95% confidence interval for mean difference in WHO bleeding, spotting and no menstrual flow indices during 90-day reference period among women randomized to Quickstart versus Conventional start of a monophasic 35 mcg EE oral contraceptive.

Indices	*Quickstart n=57*	*Conventional Start n=38*	*Mean Difference**	*95% CI** for Mean Difference*	*P-value*	*Adjusted Mean Difference****	*95% CI** for Adjusted Mean Difference*	*P-value*
Mean number of bleeding and spotting days	18.95	19.50	-0.55	-3.60; 2.49	0.72	-0.39	-3.49; 2.69	0.80
Mean number of spotting days	8.63	9.39	-0.76	-3.23; 1.70	0.54	-0.56	-3.13; 2.00	0.67
Mean number of bleeding days	10.32	10.11	0.21	-1.97; 2.39	0.85	0.16	-2.05; 2.38	0.88
Mean number of bleeding and spotting episodes	3.68	3.95	-0.26	-0.76; 0.24	0.30	-0.26	-0.76; 0.24	0.30
Mean length of bleeding and spotting episodes	5.28	5.22	0.06	-0.67; 0.79	0.87	0.09	-0.64; 0.83	0.79
Mean length of bleeding and spotting-free intervals	17.74	16.93	0.81	-1.82; 3.45	0.54	0.37	-2.23; 2.96	0.78
Mean range of bleeding and spotting-free intervals	9.91	12.84	-2.93	-6.18; 0.32	0.10	-3.16	-6.46; 0.45	0.10

* Mean differences are for (Quickstart-Conventional Start)
** CI = Confidence Interval
*** Adjusted for parity (ever vs. never given birth) and consistency of OC use (number of pills missed)

Table 5b.

Mean, mean difference and 95% confidence interval for mean difference in WHO bleeding, spotting and no menstrual flow indices during 90-day reference period among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

Indices	*Day 8+ OC Start n=45*	*Day 1-7 OC Start n=50*	*Mean Difference**	*95% CI** for Mean Difference*	*P-value*	*Adjusted Mean Difference****	*95% CI** for Adjusted Mean Difference*	*P-value*
Mean number of bleeding and spotting days	20.16	18.28	1.88	-1.04; 4.84	0.21	1.49	-1.60; 4.58	0.34
Mean number of spotting days	9.16	8.74	0.42	-2.01; 2.84	0.73	0.43	-2.14; 2.98	0.74
Mean number of bleeding days	11.00	9.54	1.46	-0.65; 3.57	0.20	1.06	-1.12; 3.25	0.34
Mean number of bleeding and spotting episodes	3.78	3.80	-0.02	-0.52; 0.47	0.93	-0.12	-0.62; 0.38	0.63
Mean length of bleeding and spotting episodes	5.42	5.11	0.31	-0.40; 1.02	0.40	0.31	-0.41; 1.03	0.40
Mean length of bleeding and spotting-free intervals	17.14	17.66	-0.52	-3.11; 2.08	0.69	-0.31	-2.97; 2.36	0.82
Mean range of bleeding and spotting-free intervals	10.38	11.72	-1.34	-4.57; 1.89	0.41	-1.73	-5.02; 1.57	0.30

* Mean differences are for (Day 8+ Start-Day 1-7 Start)
** CI = Confidence Interval
*** Adjusted for smoking (number of cigarettes per day) and consistency of OC use (number of pills missed)

Table 6a.

Summary statistics of WHO bleeding, spotting and no menstrual flow indices in 90-day reference period among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE oral contraceptive.

Indices	*Quickstart n=57*			*Conventional Start n=38*			*P-Value **
Percentile	*25th*	*50th*	*75th*	*25th*	*50th*	*75th*	
Number of bleeding/ spotting days	14.0	17.0	22.0	13.0	18.0	25.0	0.89
Number of spotting days	5.0	7.0	11.0	5.0	7.0	14.0	0.60
Number of bleeding days	7.0	10.0	14.0	6.75	9.0	13.25	0.78
Number of bleeding/ spotting episodes	3.0	3.0	4.0	3.0	4.0	5.0	0.45
Length of bleeding/spotting episodes	4.0	5.25	6.0	4.0	4.75	6.54	0.71
Length of bleeding/spotting-free intervals	12.75	18.50	22.66	12.28	17.17	21.54	0.60
Range of bleeding/ spotting-free intervals	2.0	10.0	17.0	6.0	13.5	18.0	0.10

* P-value is for comparisons of medians (50^{th} percentiles), using the Mann-Whitney *U* test.

Table 6b.

Summary statistics of WHO bleeding, spotting and no menstrual flow indices in 90-day reference period among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

Indices	*Day 8+ OC Start n=45*			*Day 1-7 OC Start n=50*			*P-Value**
Percentile	*25th*	*50th*	*75th*	*25th*	*50th*	*75th*	
Number of bleeding/ spotting days	15.0	18.0	24.0	12.0	16.0	23.25	0.12
Number of spotting days	6.0	8.0	11.0	4.75	7.0	13.0	0.64
Number of bleeding days	7.0	11.0	14.0	6.0	9.0	13.0	0.18
Number of bleeding/ spotting episodes	3.0	4.0	4.0	3.0	3.0	5.0	0.80
Length of bleeding/spotting episodes	4.5	5.6	6.0	4.0	4.60	5.96	0.16
Length of bleeding/spotting-free intervals	11.5	18.16	22.16	13.18	17.83	21.75	0.86
Range of bleeding/ spotting-free intervals	2.0	11.0	17.0	5.75	11.0	18.0	0.38

* P-value is for comparisons of medians (50^{th} percentiles), using the Mann-Whitney *U* test.

Table 7a.

Number of women experiencing WHO clinically important bleeding patterns in 90-day reference period among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE oral contraceptive.

Clinically Important Bleeding Patterns	*Quickstart n(%) n=57*	*Conventional Start n(%) n=38*	*P-value**
Amenorrhea[1]			
Yes	0	0	--
No	57 (100)	38 (100)	
Infrequent Bleeding[2]			
Yes	1 (1.8)	0	1.0
No	56 (98.2)	38 (100)	
Frequent Bleeding[3]			
Yes	11 (19.3)	11(28.9)	0.40
No	46 (80.7)	27 (71.1)	
Irregular Bleeding[4]			
Yes	13 (22.8)	12 (31.6)	0.48
No	44 (77.2)	26 (68.4)	
Prolonged Bleeding[5]			
Yes	12 (21.1)	9 (23.7)	0.96
No	45 (78.9)	29 (76.3)	
Prolonged and Frequent			
Yes	2 (3.5)	3 (7.9)	0.64
No	55 (96.5)	35 (92.1)	
Prolonged and Infrequent			
Yes	0	0	--
No	57 (100)	38 (100)	
Prolonged and Irregular			
Yes	3 (5.3)	4 (10.5)	0.58
No	54 (94.7)	34 (89.5)	
Overall Bleeding Pattern			
Acceptable[6]	27 (47.4)	16 (42.1)	0.77
Altered[7]	30 (52.6)	22 (57.9)	

(1) Amenorrhea: no bleeding during the entire reference period; (2) infrequent bleeding: fewer than 2 bleeding/spotting episode; (3) frequent bleeding: more than 4 bleeding/spotting episodes; (4) irregular bleeding: a range of bleeding-free intervals exceeding 17 days; (5) prolonged bleeding: at least one bleeding/spotting episode lasting 10 or more days; (6) acceptable bleeding: none of the above-mentioned patterns (a pattern with 2-4 bleeding spotting episodes, none lasting 10 days or more, with a range of bleeding free intervals not exceeding 17 days); and (7) altered bleeding pattern: at least one of the above-mentioned patterns.

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 7b

Number of women experiencing WHO clinically important bleeding patterns in 90-day reference period among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

Clinically Important Bleeding Patterns	*Day 8+ OC Start n(%) n=45*	*Day 1-7 OC Start n(%) n=50*	*P-value**
Amenorrhea[1]			
Yes	0	0	--
No	45 (100)	50 (100)	
Infrequent Bleeding[2]			
Yes	1 (2.2)	0	0.96
No	44 (97.8)	50 (100)	
Frequent Bleeding[3]			
Yes	9 (20.0)	13 (26.0)	0.65
No	36 (80.0)	37 (74.0)	
Irregular Bleeding[4]			
Yes	10 (22.2)	15 (30.0)	0.53
No	35 (77.8)	35 (70.0)	
Prolonged Bleeding[5]			
Yes	10 (22.2)	11 (22.0)	1.0
No	35 (77.8)	39 (78.0)	
Prolonged and Frequent			
Yes	2 (4.4)	3 (6.0)	1.0
No	43 (95.6)	47 (94.0)	
Prolonged and Infrequent			
Yes	0	0	--
No	45 (100)	50 (100)	
Prolonged and Irregular			
Yes	3 (6.7)	4 (8.0)	1.0
No	42 (93.3)	46 (92.0)	
Overall Bleeding Pattern			
Acceptable[6]	21 (46.7)	22 (44.0)	0.96
Altered[7]	24 (53.3)	28 (56.0)	

(1) Amenorrhea: no bleeding during the entire reference period; (2) infrequent bleeding: fewer than 2 bleeding/spotting episode; (3) frequent bleeding: more than 4 bleeding/spotting episodes; (4) irregular bleeding: a range of bleeding-free intervals exceeding 17 days; (5) prolonged bleeding: at least one bleeding/spotting episode lasting 10 or more days; (6) acceptable bleeding: none of the above-mentioned patterns (a pattern with 2-4 bleeding spotting episodes, none lasting 10 days or more, with a range of bleeding free intervals not exceeding 17 days); and (7) altered bleeding pattern: at least one of the above-mentioned patterns.

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 8a.

Perceptions of bleeding change in 90-days after OC initiation among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE OC.

	Quickstart *n=57* *n(%)*	*Conventional Start* *n=38* *n(%)*	*P-value**
Change in bleeding			
No change in bleeding	8 (14.0)	3 (7.9)	
Good change in bleeding	38 (66.7)	30 (78.9)	0.42
Bad change in bleeding	11 (19.3)	5 (13.2)	
Number of days of bleeding			
Same	10 (17.6)	7 (18.4)	
Less	39 (68.4)	26 (68.4)	0.99
More	8 (14.0)	5 (13.2)	
Amount of blood loss			
Same	8 (14.0)	5 (13.2)	
Less	47 (82.5)	31 (81.6)	0.92
More	2 (3.5)	2 (5.2)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected).

Table 8b.

Perceptions of bleeding change in 90-days after OC initiation among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

	Day 8+ OC Start n=45 n(%)	*Day 1-7 OC Start n=50 n(%)*	*P-value**
Change in bleeding			
No change in bleeding	6 (13.3)	5 (10.0)	
Good change in bleeding	30 (66.7)	38 (76.0)	0.60
Bad change in bleeding	9 (20.0)	7 (14.0)	
Number of days of bleeding			
Same	8 (17.8)	9 (18.0)	
Less	29 (64.4)	36 (72.0)	0.45
More	8 (17.8)	5 (10.0)	
Amount of blood loss			
Same	8 (17.8)	5 (10.0)	
Less	35 (77.8)	43 (86.0)	0.53
More	2 (4.4)	2 (4.0)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected).

Table 9a.

Number of women satisfied with OCs and continuing use after 90 days among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE OC.

	Quickstart n=57 n(%)	*Conventional Start n=38 n(%)*	*P-value**
Overall satisfaction with the pill			
Satisfied	54 (95)	36 (95)	1.0
Unsatisfied	3 (5)	2 (5)	
Would you make the same decision to start the pill?			
Yes	53 (93)	36 (95)	1.0
No	4 (7)	2 (5)	
Continuing pill use after completion of study?			
Yes	44 (77)	29 (76)	1.0
No	13 (23)	9 (24)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 9b.

Number of women satisfied with OCs and continuing use after 90 days among women initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

	Day 8+ OC Start n=45 n(%)	*Day 1-7 OC Start n=50 n(%)*	*P-value**
Overall satisfaction with the pill			
Satisfied	42 (93)	48 (96)	0.67
Unsatisfied	3 (7)	2 (4)	
Would you make the same decision to start the pill?			
Yes	41 (91)	48 (96)	0.41
No	4 (9)	2 (4)	
Continuing pill use after completion of study?			
Yes	34 (76)	39 (78)	0.81
No	11 (24)	11 (22)	

* P-value is for comparisons of proportions, using the chi-square test (continuity corrected) or Fisher's exact test where appropriate.

Table 10.

Mean number of bleeding/spotting days per pill cycle, excluding bleeding or spotting continuous with previous withdrawal bleed, among women randomized to Quickstart versus Conventional Start of a monophasic 35 mcg EE oral contraceptive and among initiating use of a monophasic 35 mcg EE oral contraceptive on menstrual cycle Day 8+ versus menstrual cycle Day 1-7.

	N	*Pill Cycle 1*	*Pill Cycle 2*	*Pill Cycle 3*
Quickstart	57	7.4	5.8	5.3
Conventional Start	38	8.1	5.4	5.5
Day 8+ Start	45	8.0	5.8	5.3
Day 1-7 Start	50	7.4	5.4	5.4

Table 11a.

Mean number of bleeding/spotting days in the 90-day follow-up period in all subjects by ever/never missed pills.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Never missed pill	22	16.18	7.82	8.36
Ever missed pill	73	20.07	9.27	10.79
P-value		0.03	0.31	0.05

Table 11b.

Mean number of bleeding/spotting days in the 90-day follow-up period in the intervention group for intention-to-treat analysis (Quickstart) by ever/never missed pills.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Never missed pill	14	16.71	8.21	8.50
Ever missed pill	43	19.67	8.77	10.91
P-value		0.18	0.75	0.10

Table 11c.

Mean number of bleeding/spotting days in the 90-day follow-up period in the control group for intention-to-treat analysis (Conventional Start) by ever/never missed pills.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Never missed pill	8	15.25	7.13	8.13
Ever missed pill	30	20.63	10.00	10.63
P-value		0.08	0.26	0.30

Table 11d.

Mean number of bleeding/spotting days in the 90-day follow-up period in the intervention group for the start-day analysis (Day 8+ OC Start) by ever/never missed pills.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Never missed pill	10	17.90	7.40	10.50
Ever missed pill	35	20.80	9.66	11.14
P-value		0.26	0.30	0.70

Table 11e.

Mean number of bleeding/spotting days in the 90-day follow-up period in the control group for the start-day analysis (Day 1-7 OC Start) by ever/never missed pills.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Never missed pill	12	14.75	8.17	6.58
Ever missed pill	38	19.39	8.92	10.47
P-value		0.06	0.70	0.04

Table 12a.

Mean number of bleeding/spotting days in the 90-day follow-up period in all subjects by parity.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Nulliparous	81	19.77	9.33	10.43
Parous	14	15.71	6.64	9.07
P-value		0.05	0.12	0.37

Table 12b.

Mean number of bleeding/spotting days in the 90-day follow-up period in the intervention group (Quickstart) by parity.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Nulliparous	46	19.48	8.87	10.61
Parous	11	16.73	7.64	9.09
P-value		0.25	0.52	0.34

Table 12c.

Mean number of bleeding/spotting days in the 90-day follow-up period in the control group (Conventional Start) by parity.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Nulliparous	35	20.14	9.93	10.20
Parous	3	12.00	3.00	9.00
P-value		0.09	0.07	0.74

Table 13a.

Mean number of bleeding/spotting days in the 90-day follow-up period in all subjects by smoking status.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Non-smoker	79	19.14	9.14	10.00
Smoker	16	19.31	7.94	11.38
P-value		0.93	0.46	0.34

Table 13b.

Mean number of bleeding/spotting days in the 90-day follow-up period in the intervention group (Day 8+ OC Start) by smoking status.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Non-smoker	39	20.74	9.49	2.42
Smoker	6	16.33	7.00	4.69
P-value		0.16	0.35	0.33

Table 13c.

Mean number of bleeding/spotting days in the 90-day follow-up period in the control group (Day 1-7 OC Start) by smoking status.

	N	*Mean number of bleeding and spotting days*	*Mean number of spotting days*	*Mean number of bleeding days*
Non-smoker	40	17.58	8.80	8.78
Smoker	10	21.10	8.50	12.60
P-value		0.18	0.89	0.06

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8.0 Appendices

8.1 Definitions

Bleeding: Bloody vaginal discharge that requires sanitary protection (pads or tampons).

Spotting: Bloody vaginal discharge that requires use of a "panty-liner" only or does not require sanitary protection.

Bleeding day: A day on which bleeding occurs.

Spotting day: A day on which spotting occurs.

Bleeding/spotting episode: Set of one or more bleeding/spotting days, bounded at each end by two or more bleeding/spotting-free days. A single day of bleeding/spotting preceded and followed by bleeding/spotting-free intervals is considered as a bleeding/spotting episode.

Bleeding/spotting-free day: A day on which neither bleeding nor spotting occurs.

Bleeding/spotting-free interval: Set of two or more consecutive bleeding/spotting-free days, bounded at each end by bleeding/spotting days. A single day free of bleeding/spotting preceded and followed by bleeding/spotting episodes is considered as part of the bleeding/spotting episode.

Amenorrhea: No bleeding in the 90-day reference period.

Infrequent bleeding: Fewer than two bleeding/spotting episodes in the 90-day reference period.

Frequent bleeding: More than four bleeding/spotting episodes in the 90-day reference period.

Irregular bleeding: A range of lengths of bleeding/spotting-free intervals exceeding 17 days in the 90-day reference period.

Prolonged bleeding: At least one bleeding/spotting episode lasting 10 days or more in the 90-day reference period.

Altered vaginal bleeding pattern: One or more of the following bleeding patterns in the 90-day reference period: amenorrhea, infrequent, frequent, irregular or prolonged bleeding.

Acceptable vaginal bleeding pattern: Vaginal bleeding pattern not included in the definition of altered vaginal bleeding pattern.

Increased vaginal bleeding pattern: Subjective appreciation for an increase of the menses in quality or quantity, comparing 90-days post-OC initiation with pre-OC initiation.

Decreased vaginal bleeding pattern: Subjective appreciation for an decrease of the menses in quality or quantity, comparing 90-days post-OC initiation with pre-OC initiation.

8.2 Telephone screening form

Name_____ **Date**_____

Phone #s_____ **Screened by**_____

Best time to call_____

1.	How did you hear about the study?		
2.	How old are you?	_____	If <18 or >35, **EXCLUDE**
3.	How often do you get your period?		If <21 or >35 days, **EXCLUDE**
4.	Ever used birth control pills/injectable/EC before?	Yes No	If yes, OC, Inj, and/or EC?
	→ If yes, when was the last time? → How many normal periods in addition to withdrawal bleed since stopping/last use of birth control pill/injectable/EC?	___/___/___	If currently using, **EXCLUDE**
5.	Are you willing to use Ortho-Novum 1/35?	Yes No	If no, **EXCLUDE**
6.	Are you willing to be randomly assigned to a day to start the pill?	Yes No	If no, **EXCLUDE**
7.	Do you have any medical/health problems? (e.g. high blood pressure)	Yes No	Explain:
8.	Are you currently taking any medications?	Yes No	Explain:
9.	Are you sexually active? When did you last have sexual intercourse? What, if anything, are you currently using for birth control? What, if anything, did you use at last sex?	Yes No ___/___/___	
10.	Have you ever been pregnant? How did your last pregnancy end? When did your last pregnancy end?	Yes No ___/___/___	
Notes:			

8.3 In-person enrollment clinical screening form

New York Presbyterian Hospital
ACNC/FPC/SBC
ECP/QUICK START

MRN:

NAME:

DATE: _____ TIME: _____ D.O.B.: SEX:

ECP: UNPROTECTED SA - DATE:_____ TIME:_____ HRS. SINCE SA:_____
Previous unprotected intercourse: ❒ Yes ❒ No

Urine Pregnancy Test Result: ❒ Positive ❒ Negative
LMP: _____ PMP: _____ BP: _____ WEIGHT: _____

Date of Last Physical Exam: _____
Current Method: ❒ None How Long/What?: _____
Method Desired: _____

MEDICAL HISTORY	FAMILY	PATIENT	DETAILS (Specify Contraindications if any)
MI < 50 ys. Thrombophlebitis			
Stroke			
High blood pressure	X		
Hepatitis - current	X		
Cancer	X		
Diabetes	X		
Gallbladder disease	X		
Epilepsy	X		
Migraine headaches	X		
Smoking	X		usage/day:

Physical Exam: ❒ Not Needed Today ❒ Deferred Until: _____ ❒ Done - See Reverse

ASSESSMENT:

CANDIDATE FOR:	❒ Yes ECP	❒ No	❒ Yes O.C.	❒ No
Correct Usage Reviewed:	❒ Yes	❒ No	❒ Yes	❒ No
Side Effects:	❒ Yes	❒ No	❒ Yes	❒ No
Fact Sheet Given:	❒ Yes	❒ No	❒ Yes	❒ No
Consent Signed:	❒ Yes	❒ No	❒ Yes	❒ No
Foam/Condom x min. 1 wk.:	❒ Yes	❒ No	❒ Yes	❒ No
HIV/STD Prevention	❒ Yes	❒ No	❒ Yes	❒ No
Patient Verbalized Understanding:	❒ Yes	❒ No	❒ Yes	❒ No

PLAN: ECP Given/Lot #: _____ OC Given/Brand/Lot #: _____ # Packs: _____
First Dose Taken in Clinic: ❒ Yes ❒ No

1) RTC Date: _____
2) Reminder Given Re: 4 wk. appointment: ❒ Yes ❒ No

_____
Signature

NEW YORK PRESBYTERIAN HOSPITAL
Columbia Presbyterian Center

CONTINUATION SHEET

IF NO PLATE, PRINT NAME, SEX AND MEDICAL RECOR

8.4 Study participation consent form

Columbia-Presbyterian Medical Center - Consent to Participate in a Research Study

The purpose of this consent form is to provide you with the information you need to consider in deciding whether to participate in this research study.

STUDY TITLE: Study of a novel oral contraceptive initiation method: assessment of bleeding outcomes

Purpose of the Study You are invited to participate in a research study of two different ways of starting oral contraceptives (the "pill"). One way is to wait until your period comes to start taking the pill. The other way is to start the pill right away, without waiting for your period. Although we have already been using both ways of starting the pill, we don't know if one way is better than another.

You were selected as a possible participant in this study because you are interested in using the pill as a contraceptive method.

Study Procedures If you decide to participate, you will receive a routine assessment, including health history, physical and pelvic examination, a Pap test (if you have not had one recently), and a pregnancy test. We will ask you questions for about 10 minutes about any past contraceptive use or any pregnancies. You will be given a 4-month supply of birth control pills, with instructions for use. The pill you will be given is Ortho-Novum®1/35, which is an approved oral contraceptive. The research staff will decide which way you will start the pill by selecting a blank envelope from a box. Inside the envelope, there will be instructions about one way to start the pill. You will be asked to start the pill according to instructions from the research staff. We will give you a card today to mark any days that you have bleeding or spotting during the next three months. Every month, you will return the card to us, either by mailing it or by dropping it off in the Family Planning clinic, or faxing it to the clinic. Someone will call you to remind you to return the diary card. After 3-4 months you will have a final visit. At this time, we will collect the diary card, arrange to mail you a check for your compensation, and refer you for further family planning care, if desired.

Study Discomforts and Risks Your participation is this study does not involve any risks. Starting the pill may cause you to have a different bleeding pattern. If this occurs, it won't be dangerous, but it may be annoying. Marking the bleeding calendar every day will take a few seconds of your time.

The most common side effects of birth control pills include nausea, vomiting, dizziness, rash, depression, change in appetite, possibly permanent spotting or darkening of the skin, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty in wearing contact lenses.

The serious side effects of birth control pills occur very seldom. These conditions include: gall bladder disease; high blood pressure; liver tumors; forming blood clots in the blood vessels of the legs, lungs, brain, heart, or other organs of the body, possibly leading to stroke heart attack, pulmonary embolism, or blindness. Cigarette smoking may increase the risk of heart and blood vessel disease from using birth control pills.

The results of research studies about the effect of birth control pills on breast cancer do not agree. Most studies have not found an increase in breast cancer. However, some studies have reported that there is an increased risk, particularly in younger women.

Study Benefits You may or may not benefit personally from this study. Benefits to you may include quicker contraceptive protection. Benefits to society may include improved understanding of how to use the pill most effectively.

Alternative Procedures You may use the pill as your contraceptive without participating in this study and without keeping the bleeding diary. You may speak to your provider about choosing any method of birth control you desire.

Costs and Compensation There will be no costs to you. We will reimburse you $1 per day for

every day of the bleeding diary you complete. If you complete the entire 90-day diary, you will receive an additional bonus of $50 for a total maximum compensation of $140. Your compensation will be paid by check, which you will receive approximately 4-6 weeks after completing the study.

Confidentiality Any information obtained during this study and identified with you will remain confidential. You understand that your medical records may be examined by FDA representatives. Your participation in this study is completely voluntary. You can refuse to participate or withdraw from the study at any time and such a decision will not affect your medical care at Columbia-Presbyterian Medical Center now or in the future. Signing this form does not waive any of your legal rights. Any new findings that may affect your willingness to continue in this study will be communicated to you.

Questions If you have any questions, please ask, and we will do our best to answer them. If you have additional questions in the future, you can reach Dr. Westhoff or Dr. Murphy at 212-342-3208. If you have any questions on your rights as a research subject, you can call the Institutional Review Board at 212-305-5883 for information.

Statement of Consent

I have discussed this study with Dr. Westhoff , Dr. Murphy, or their collaborators to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigators, Dr. Westhoff or Dr. Murphy, at 212-342-3208 or the Institutional Review Board, at 212-305-5883 so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a. The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital;
b. I will be responsible for the cost of such care, either personally or through my medical insurance or other form of medical coverage.
c. No monetary compensation for wages lost as a result of injury will be paid to me by the Columbia-Presbyterian Medical Center, and;
d. I will receive a copy of this consent form.

Signatures:

_____ _____
Participant Date

_____ _____
Investigator eliciting consent Date

The solicitation of subjects into this study has been approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

8.5 Oral contraceptive consent form

The Presbyterian Hospital in the City of New York
Columbia-Presbyterian Medical Center
New York, New York 10032-3784

ORAL CONTRACEPTIVE CONSENT FORM

I agree that I am receiving birth control Pills of my own free will. Pills are the method of family planning which I have chosen from all the methods that have been explained to me. The advantages and disadvantages of the other methods of birth control have been explained to me.

I understand and agree to have the clinic examine me and perform the necessary tests, including lab work; I also agree to appropriate treatment if indicated. I understand that if any of my test results are abnormal, you will be contacting me. I am aware, that it is my responsibility to follow your instructions.

BENEFITS: I am aware that oral contraceptives are not guaranteed to be 100% effective. It is my understanding that combined birth control Pills can be 99% effective if I take them exactly according to instructions. I understand that many women experience the following benefits from using birth control Pills.

- Decreased menstrual cramps
- Decreased menstrual bleeding
- More regular menstrual bleeding
- Improvement in acne
- Less risk of cancer of the uterus or ovary

RISKS: I have been told to watch out for the following danger signals and to return to the clinic or call my clinician at once if I develop one of these problems. These could be warnings of serious or even life-threatening illness.

PILL DANGER SIGNS

	A	• Abdominal pain (severe)
	C	• Chest pain (severe), cough, shortness of breath
CAUTION	H	• Headache (severe), dizziness, weakness, or numbness
	E	• Eye problems (vision loss or blurring) speech problems
	S	• Severe leg pain (calf or thigh)

See your clinician if you have any of these problems, or if you develop yellow jaundice or a breast lump. I have been told that most of the serious problems in Pill users happen to women over 35 who are heavy smokers (10 or more cigarettes a day), or who have high blood pressure.

POSSIBLE SIDE EFFECTS

I am aware that while using oral contraceptives, I could have the following side effects, many of which can be temporary:

Major Problems (1/5000 women)
- Blood clot of the leg or the lung
- Stroke or heart attack
- Gallbladder disease

Minor Problems (1/20 women)
- Nausea
- Spotting between periods
- Less menstrual bleeding
- Breast tenderness
- Weight changes
- Headache
- Mood changes

INSTRUCTIONS for the use of birth control Pills have been given to me in writing and I have been given a patient package insert for my specific brand of Pill. No guarantee or assurance has been made to me as to the results of using this method. I understand that neither the provider nor the hospital are in any way responsible should I become pregnant.

QUESTIONS: I have been given the chance to ask questions about all forms of birth control ~~and about~~ the Pill in particular. My questions have been answered to my satisfaction.

Witness _____ Patient _____

Date: _____ Date: _____

9/23/98

The Presbyterian Hospital in the City of New York
Columbia-Presbyterian Medical Center
New York, New York 10032-3784

FORMA DE CONSENTIMIENTO PARA CONTRACEPTIVOS ORAL

Estoy de acuerdo que recibo las Píldoras de control de la natalidad de mi propia voluntad. Las píldoras son e método de planificación familiar de cual he escogido sobre todos los métodos de control de la natalidad que me han explicado. Me han explicado las ventajas y desventajas de este método.

Entiendo y estoy de acuerdo que la clínica me examine y me hagan las pruebas necesarias, incluyendo esos d laboratorio. También estoy de acuerdo al tratamiento apropiado, si está indicado. Entiendo que si algunos resultadc de las pruebas son anormal, usted se pondrá en contacto conmigo. Estoy enterada que es mi responsabilidad de seguir sus instrucciones.

BENEFICIOS: Estoy enterada que los anticonceptivos orales no son garantizados a ser 100% efectivo. Es mi entendimiento que las Píldoras combinadas de control de la natalidad pueden ser 99% efectivo si las tomo exactamente de acuerdo a las instrucciones. Entiendo que algunas mujeres sienten los siguientes beneficios cuando usan la Píldora de control de la natalidad.

- Reducido dolor menstrual
- Reducido sangramiento menstrual
- Sangramiento menstrual más regular
- Mejoramiento del acné
- Menos riesgo de cancer del útero o del ovario

RIESGOS: Me han dicho que tengo que velar por las siguientes señales de peligro y de regresar a la clínica ponerme en contacto con mi clínica de una vez, si se desarrollan uno de estos problemas. Estas pueden ser advertencias de enfermedades serias o hasta amenaza de vida.

PRINCIPIO DE SEÑALES DE PELIGRO DE LA PÍLDORA

PRECAUCIÓN	P	• Pecho (dolor severo), tos, falta de aliento
	E	• Entumecimiento, dolores severos de cabeza, mareos o decaimiento
	N	• No puedes ver o vista borrosa, problemas del lenguaje
	A	• Abdomen (vientre (dolor severo)
	S	• Severo dolor en las piernas (pantorrilla o muslo)

Vea a su médico si tienes cualquier de estos problemas, o si desarrolla ictericia amarilla o masa en el seno. Me han dicho que la mayor parte de los problemas serios en las quien usan la Píldora pasan a mujeres mayores de 35 años fuman mucho (10 o más cigarrillos al día) o que tienen la presión alta.

POSIBLES EFECTOS SECUNDARIOS

Yo estoy enterada que mientras uso las píldoras puedo sentir los siguientes efectos de los cuales muchos so temporales:

PROBLEMAS MAYORES (1/5000 mujeres)

- Coágulo de sangre en la pierna o el pulmón
- Ataque fulminante o ataque del corazón
- Enfermedad de la vesícula biliar

PROBLEMAS MENORES (1/20 mujeres)

- Náusea
- Manchando entre periodos
- Menos sangramiento menstrua
- Senos sensibles
- Aumento de peso
- Dolor de cabeza
- Cambios de humor

INSTRUCCIONES sobre el uso de la Píldora anticonceptiva me lo han dado por escrito y me han dado una hoja la paciente del paquete para mi marca específica de Píldora. Ninguna garantía o seguridad me han dado sobre el resultado del uso de este método. Entiendo que ni el proveedor, ni el hospital están en cualquier manera ons si caigo embarazada.

PREGUNTAS: Me han dado la oportunidad de preguntar sobre todas las formas de control de la natalidad y sobre la Píldora en particular. Mis preguntas fueron contestadas a mi satisfación.

Testigo _____ Paciente _____

Fecha: Fecl

8.6 Baseline enrollment questionnaire

Date of enrollment: _____

Study ID Number: _____

A. BACKGROUND INFORMATION

1.	What is your date of birth?	____|____|____ month day year
2.	How old are you?	_____
3.	What is your height?	_____|_____ feet inches
4.	How much do you weigh?	_____
5.	What is your racial or ethnic group? Hispanic..... African-American..... White..... Asian..... Other.....	 1 2 3 4 5
6.	Are you employed? yes..... no.....	 1 2
6a.	If yes, How many hours per week do you work?	_____
7.	Are you a student? yes..... no.....	 1 2
8.	Do you smoke cigarettes? yes..... no.....	 1 2
8a.	If yes, How many per day?	_____

B. CONTRACEPTIVE HISTORY

9.	Have you ever taken the pill before? yes..... no.....	 1 2
9a.	If yes, When was the last time you took a pill?	_____|_____ month year
9b.	What was the name of the pill?	_____
9c.	How long did you use the pill?	_____|_____ months years
9d.	Why did you stop taking the pill?	
10.	Have you ever used emergency contraception? yes..... no.....	 1 2
10a.	If yes, Have you used it since your last menstrual period? yes..... no.....	 1 2

C. PREGNANCY INFORMATION

11.	Have you ever been pregnant? yes..... no.....	 1 2
11a.	If yes, How many times have you been pregnant?	_____
11b.	How many births?	_____
11c.	How many miscarriages?	_____
11d.	How many terminations?	_____
11e.	How many other ends?	_____
11f.	How did your most recent pregnancy end? birth..... miscarriage..... termination..... other.....	 1 2 3 4
11g.	When did your most recent pregnancy end?	____|____|____ month day year

D. MENSTRUAL HISTORY

12.	What was the first day of your last menstrual period?	____|____|____ month day year
13.	What was the first day of your previous menstrual period?	____|____|____ month day year
14.	In the last 12 months, what was your cycle length? (first day of one period to the first day of next period)	_____ _____
15.	In the last 12 months, did you have any spotting between menses? yes..... no.....	 1 2

E. PARTNER INFORMATION

16.	Do you currently have a partner? yes..... no.....	 1 2
16a.	If yes, Do you have... 1 partner..... more than 1 partner.....	 1 2
16b.	How long have you been with your main partner?	_____ | _____ months years
16c.	How old is your main partner?	_____
16d.	Are you sexually active with your main partner? yes..... no.....	 1 2
16e.	How long have you been sexually active with you main partner?	_____ | _____ months years
16f.	Have you discussed birth control with him? yes..... no.....	 1 2
16g.	Have you told him about your plan to use the pill? yes..... no.....	 1 2
16h.	How do you think he would feel about you using the pill? Would he... strongly approve..... approve..... disapprove..... strongly disapprove..... have no opinion.....	 1 2 3 4 5
16i.	How satisfied are you in your relationship with him? very satisfied..... somewhat satisfied..... somewhat dissatisfied..... very dissatisfied.....	 1 2 3 4

F. MENSTRUAL DISTRESS (MDQ)

For questions 17-18, use the following scale:

0 = no experience of symptom
1 = present, mild
2 = present, moderate
3 = present, strong
4 = present, severe

17.	Describe your experience of the following symptoms or feelings for your most recent flow: Muscle stiffness..... Headache..... Cramps..... Backache..... Fatigue..... General aches and pains.....	
18.	Describe your experience of the following symptoms or feelings today: Muscle stiffness..... Headache..... Cramps..... Backache..... Fatigue..... General aches and pains.....	

G. DEPRESSION SCALE (CES-D, 1977)

Questions 19-38 refer to ways you might have felt or behaved. Use this scale to describe how often you felt this way during the past week.

0 = rarely or none of the time (less than 1 day)
1 = some or a little of the time (1-2 days)
2 = occasionally or a moderate amount of the time (3-4 days)
3 = most or all of the time (5-7 days)

19.	I was bothered by things that usually don't bother me.....	
20.	I did not feel like eating; my appetite was poor.....	
21.	I felt that I could not shake off the blues even with help from my family or friends.....	
22.	I felt that I was just as good as other people.....	
23.	I had trouble keeping my mind on what I was doing.....	
24.	I felt depressed.....	
25.	I felt that everything I did was an effort.....	
26.	I felt hopeful about the future.....	
27.	I thought my life had been a failure.....	
28.	I felt fearful.....	
29.	My sleep was restless.....	
30.	I was happy.....	
31.	I talked less than usual.....	
32.	I felt lonely.....	
33.	People were unfriendly.....	
34.	I enjoyed life.....	
35.	I had crying spells.....	
36.	I felt sad.....	
37.	I felt that people dislike me.....	
38.	I could not get "going".....	

8.7 Follow-up exit questionnaire

Date:_____

Study ID Number:_____

A. Pill Usage

1.	When did you take the first pill?	
2.	When was the last day (date) that you took a pill?	
3.	How many pills in all have you taken? *(fill in calendar days)*	
4.	About how many times did you forget to take 1 pill and then remember the next day?	
5.	About how many times did you forget to take 2 or more pills in a row?	
6.	Would you say that your experiences with the pill have been better, worse, or the same as you expected? better..... worse..... same.....	 1 2 3
6a.	If (better/worse), Why?	
7.	The following are some experiences that many women have, whether or not they take the pill. When you took the pill...	

	No	Good	Bad
7a. Did you have any weight change?.....	1	2	3
7b. Did you have any change in bleeding?.....	1	2	3
7c. Did you have any change in headaches.?.....	1	2	3
7d. Did you have any change in breast tenderness?.....	1	2	3
7e. Did you have any change in mood?.....	1	2	3
7f. Did you have any change in acne?.....	1	2	3
7g. Did you have any change in hair?.....	1	2	3
7h. Did you have any change in appetite?.....	1	2	3
7i. Did you have any change in nausea?.....	1	2	3

8.	Since you have been taking the pill, has the number of days of bleeding been...	
	more..... less..... same.....	1 2 3
9.	Since you have been taking the pill, has the amount of blood flow been...	
	more..... less..... same.....	1 2 3

10.	How satisfied overall have you been with the pill? very satisfied..... somewhat satisfied..... somewhat unsatisfied..... very unsatisfied.....	 1 2 3 4
11.	I first spoke with you on_____. If you could go back to that date, do you think you would make the same decision and use the pill? yes..... no.....	 1 2
12.	Would you describe yourself as someone who is using the pill or someone who is not using the pill? using the pill..... not using the pill.....	 1 (skip to 15a) 2
13.	If you've stopped using the pill, Why did you stop?	
14.	What would you say is the MAIN reason you stopped?	
15.	Do you plan to use the pill in the future? yes..... no.....	 1 2 (skip to 16)
15a.	If yes, When do you plan to take the next pill? today..... tomorrow..... Sunday..... when I get my period..... when my bleeding stops..... when my partner returns from_____..... don't plan to take another pill..... other_____..... when sexually active..... when go back to doctor.....	 1 2 3 4 5 6 7 (back to 13, 14) 8 9 10

B. Visits

16.	Since I first talked to you, have you been to any clinic or hospital? yes..... no.....	 1 2
16a.	If yes, What for?	

C. Sexual Activity and Exposure

17.	I spoke with you first on _____. Since then, have you had sex? yes..... no.....	 1 2 (skip to 22)
17a.	If yes, You answered some questions before about your partner. Are you having sex with the same person you talked about or with someone new? same person..... new person.....	 1 (skip to 18) 2
17b.	If yes, Does he know you're using the pill? yes..... no.....	 1 2
17c.	How do you think he (feels/would feel) about you using the pill? (Does/Would) he... strongly approve..... approve..... disapprove..... strongly disapprove..... no opinion.....	 1 2 3 4 5
17d.	Does he want you to become pregnant in the next 6 months? yes..... no.....	 1 2
18.	When was the last day (date) you had sex?	
19.	How many times have you had sex since I first spoke with you?	

**IF LPD<LSD, ASK 20-21*

20.	Have you used any condoms (or any other method) since (LAST PILL DATE)? Yes depo..... IUD..... norplant..... condoms..... withdrawal..... spermicide..... ECP..... No.....	 1 2 3 4 5 6 7 8
21.	If yes, How often did you use them? Did you use them... all of the time..... some of the time..... at least one time.....	 1 2 3

D. Pregnancy

22.	When was the first day (date) of your last menstrual period?	
23.	If >4 weeks, Do you think you might be pregnant? yes..... no.....	 1 2
23a.	Why?	

E. Menstrual Distress (MDQ)

	For questions 24-25, use the following scale: **0 = no experience of symptom** **1 = present, mild** **2 = present, moderate** **3 = present, strong** **4 = present, severe**	
24.	Describe your experience of the following symptoms or feelings for your most recent flow: Muscle stiffness..... Headache..... Cramps..... Backache..... Fatigue..... General aches and pains.....	
25.	Describe your experience of the following symptoms or feelings today: Muscle stiffness..... Headache..... Cramps..... Backache..... Fatigue..... General aches and pains.....	

F. Depression Scale (CES-D, 1977)

	Questions 19-38 refer to ways you might have felt or behaved. Use this scale to describe how often you felt this way <u>during the past week.</u> **0 = rarely or none of the time (less than 1 day)** **1 = some or little of the time (1-2 days)** **2 = occasionally or a moderate amount of the time (3-4 days)** **3 = most or all of the time (5-7 days)**
26.	I was bothered by things that usually don't bother me.....
27.	I did not feel like eating; my appetite was poor.....
28.	I felt that I could not shake off the blues even with help from my family or friends.....
29.	I felt that I was just as good as other people.....
30.	I had trouble keeping my mind on what I was doing.....
31.	I felt depressed.....
32.	I felt that everything I did was an effort.....
33.	I felt hopeful about the future.....
34.	I thought my life had been a failure.....
35.	I felt fearful.....
36.	My sleep was restless.....
37.	I was happy.....
38.	I talked less than usual.....
39.	I felt lonely.....
40.	People were unfriendly.....
41.	I enjoyed life.....
42.	I had crying spells.....
43.	I felt sad.....
44.	I felt that people dislike me.....
45.	I could not get "going".....

8.8 Sample 90-day bleeding diary

	Sun	Mon	Tues	Weds	Thurs	Fri	Sat
January	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
February	28	29	30	31	1	2	3

	Sun	Mon	Tues	Weds	Thurs	Fri	Sat
	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
March	25	26	27	28	1	2	3

	Sun	Mon	Tues	Weds	Thurs	Fri	Sat
	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31

	Sun	Mon	Tues	Weds	Thurs	Fri	Sat
April	1	2	3	4	5	6	7
	8	9	10	11	12	13	14

Circle day of OC start and day 90 after OC start

Record bleeding at the END of each day
- For each day of BLEEDING, write **B**
- For each day of SPOTTING, write **S**
- For each day of NO FLOW, write **N**

ID#_____

BLEEDING = loss of blood requiring use of a sanitary pad or tampon

SPOTTING = loss of blood requiring a panty liner or nothing

RECORD OF CALLS

NAME_____

Try #	Day	Date	Time	Comments

8.9 Columbia University Institutional Review Board ethical approval for study

COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

COLUMBIA-PRESBYTERIAN MEDICAL CENTER INSTITUTIONAL REVIEW BOARD
CPMC IRB

June 14, 2001

Carolyn Westoff, MD
Department of Obstetrics-Gynecology
PH 16-80

RE: CPMC IRB # 8993 "STUDY OF NOVEL ORAL CONTRACEPTIVE INITIATION METHOD:ASSESSMENT OF BLEEDING OUTCOMES"

Dear Dr. Westoff:

The research study involving human subjects described in the protocol you recently submitted for Institutional Review Board review was re-approved at the convened IRB meeting on 06/06/2001.

The IRB approves this research protocol for the period of 06/14/2001 to 06/13/2002. This date of re-approval for your protocol is the date to be used on all certification forms (including HHS Form 310) or letters forwarded to funding agencies.

Please note:

- All new participants need to sign the latest consent, dated 06/14/2001 to 06/13/2002. Enclosed with this letter: 1 Consent form.
- The CPMC IRB expiration date for this study is 06/13/2002.

We will forward renewal information to your office about 60 days prior to the study's new expiration date of 06/13/2002. To insure that approval for your study does not lapse, please submit renewal documentation at least thirty days prior to this expiration date.

All adverse events, amendments, modifications and advertisements of any type must be submitted to the IRB office for review.

Sincerely,

Paul Papagni, JD
Executive Director, CPMC IRB

PP/cw

cc: IRB File

encl: Consent form (1)
Approved ads (2)

THE CPMC IRB EXPIRATION DATE FOR THIS STUDY IS 06/13/2002

630 West 168th Street P&S 3-460 New York, NY 10032 212-305-5883 Fax 212-305-1316

COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

COLUMBIA-PRESBYTERIAN MEDICAL CENTER INSTITUTIONAL REVIEW BOARD
CPMC IRB

DATE: June 19, 2000

TO: Carolyn Westoff, MD
Department of OB/GYN
PH 16-80

Donald S. Kornfeld, MD.

FROM: Donald S. Kornfeld, M.D., Chairman, IRB

RE: **IRB RE-APPROVAL OF RESEARCH PROTOCOL CPMC IRB #8993; "STUDY OF NOVEL ORAL CONTRACEPTIVE METHOD: ASSESSMNET OF BLEEDING OUTCOMES"**

The research study involving human subjects described in the protocol you recently submitted for IRB review was re-approved at the IRB meeting held June 14, 2000.

This meeting date is the official date of approval for your protocol and is the date to be used on all certification forms (including HHS Form 310) or letters forwarded to funding agencies.

The study was re-approved for a period of *one year from the IRB meeting date mentioned in paragraph one.* We will forward the renewal forms about 6 weeks before that date.

All adverse events, amendments, modifications and advertisements of any type must be submitted to the IRB office for review.

ALL NEW SUBJECTS TO BE ENROLLED MUST SIGN THE LATEST APPROVED CONSENT FORM

P.S. The study is reactivated, as you have requested.

Per IRB policy, if you plan to enroll Spanish-speaking subjects, a Spanish Consent Form is required. Please see the attached memo.

630 West 168th Street P&S 3-460 New York, NY 10032 212-305-5883 Fax 212-305-1316

COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

COLUMBIA-PRESBYTERIAN MEDICAL CENTER INSTITUTIONAL REVIEW BOARD
CPMC IRB

February 3, 2000

Carolyn Westhoff, MD
OB/GYN
PH 16-80

RE: IRB#: 8993, "STUDY OF NOVEL ORAL CONTRACEPTIVE INITIATION METHOD: ASSESSMENT OF BLEEDING OUTCOMES,"

Dear Dr. Westhoff

Thank you for forwarding the revised consent form to be used with this study. Since the new consent form includes all the revisions requested by the IRB reviewers, the enrollment of subjects into this study is now approved. I am enclosing your **stamped IRB approved consent forms.**

The official date of the IRB approval for the study is the date of the meeting at which it was discussed and recommended for approval (March 30, 1999). The study was approved for twelve months from that date. Therefore, the next renewal application (IRB Form C) will be due in February, 2000.

Any modification of the study procedures or recruitment methods must be submitted fro IRB review before being implemented, unless it is necessary for a subject's safety.

As with all IRB protocols, any serious or excepted adverse events must be reported as they occur.

Sincerely,

Donald S. Kornfeld, MD
Chairman, CPMC IRB

DSK/bd

cc: Stephen Brown, MD

630 West 168th Street P&S 3-460 New York, NY 10032 212-305-5883 Fax 212-305-1316

8.10 Quickstart OC continuation rates study abstract

QUICKSTART: A NOVEL ORAL CONTRACEPTIVE INITIATION METHOD

Carolyn L. Westhoff, et al. 2001

Accepted for presentation at the American Public Health Association Conference, 2001
Accepted for presentation at the Association of Reproductive Health Professionals Conference, 2001

Rationale: Oral contraceptives (OCs) are conventionally initiated during a woman's menses, which often means waiting weeks after prescription to take the first pill. Many women do not begin their OCs due to confusion, ambivalence or intervening pregnancy. Taking the first pill immediately under direct observation is an alternative initiation method employed in the Columbia-Presbyterian Family Planning Clinics.

Purpose: This prospective observational study assessed continuation to the second pack of pills among women who took their first pill in the clinic compared with women instructed to start the pill conventionally.

Methods: We interviewed 250 women requesting OCs for contraception at the end of their clinic visit regarding: OC instructions, contraceptive and reproductive history, fertility motivation, and partner influence. A telephone interview, about six weeks after enrollment, used calendar recall to quantify pills taken.

Results: Participants were predominately Hispanic; their mean age was 22. 229 women (92%) completed the follow-up interview. 88% of the women who took their first pill in the clinic continued to the second pack of pills, compared with only 74% of those who started the pill conventionally (P=0.03). Also associated with continuation were age, partner knowledge of OC use and desire for pregnancy. After adjustment, women who took their first pill in the clinic remained more likely to continue (OR 2.74; 95% CI 1.1-6.8) than women who did not.

Conclusion: This approach simplifies health education, is easy to implement, and may lead to increased OC continuation, but needs to be evaluated in a randomized controlled trial.

9.0 Acknowledgements

I would like to thank Dr. Carolyn Westhoff, who served as my primary supervisor, for taking me in on Dr. Zena Stein's word, for providing me with an interesting and challenging dissertation topic, and for excellent mentoring over the last year. Her talents as both a clinician and a public health researcher are an inspiration.

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