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13. ABSTRACT *(Maximum 200 Words)*
This prospective, longitudinal study examines contraceptive outcomes among active-duty military and civilian women who receive one of three different methods of contraception (Depo-Provera, Ortho-Novum 1/35, and Ortho-Cept). Outcomes to be examined include method continuation, satisfaction, dysmenorrhea, menstrual bleeding, pregnancy rates, bone density, and plasma lipids. This summary report details the specific activities that have occurred during Year 3 of funding (September 23, 1998 to September 22, 1999). According to the SOW, 4 major objectives and related tasks were to be addressed during this period. Significant progress across each major objective was achieved. A total of 386 women (183 at WHMC and 203 at UTMB) have been successfully recruited and completed their initial visit. Follow-up visits at 3, 6, 12, 18, and 24 months were conducted on 319, 262, 191, 86, and 28 subjects respectively. Scanning of baseline data has been completed and statistical analyses have been conducted comparing demographic and reproductive characteristics as well as baseline laboratory values by site. Data collected at 6 months demonstrated discontinuation rates of 29% at UTMB and 36% at WHMC (p=.18). During Year 4, 12-month visits will be completed and outcomes will be compared by contraceptive method.

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Abby Berenson MD

PI - Signature Date

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Introduction

Operation Desert Shield/Storm involved the largest network of female soldiers from the United States ever deployed to a combat situation (1–3). Utilization data collected in one evacuation hospital found that 25% of all patient visits during the period of deployment were made by servicewomen, despite the fact that only 8% of the entire deployed force was female (2). Over 50% of all visits made by women were for gynecologic concerns as contraception, dysmenorrhea, and pelvic pain (3). In fact, 56% of medical evacuations by women were due to pregnancy (2). Relative to treatment, the continuation of or restarting of oral contraceptive pills and related bleeding disorders represented the largest number of gynecological complaints treated by this facility (3). These data demonstrate the critical need to determine the safest, most convenient, and most effective contraceptive method for women serving in the Armed Forces.

Two alternative forms of contraception which may be appropriate for use by servicewomen have recently been approved for use in the United States. In the past, most servicewomen requesting contraception have been prescribed a monophasic norethindrone-containing birth control pill (NOCA). In 1992, injectable depot medroxyprogesterone acetate (DMPA) received approval and more recently, birth control pills using the new progestin, desogestrel (DOCA), have been made available in the United States (12-14). As described below, these new formulations, when compared with the pill traditionally prescribed for servicewomen, may increase contraceptive efficacy and long-term continuation rates, as well as minimize dysmenorrhea and menstrual bleeding irregularities.

DMPA is an injectable progestational agent that offers a highly effective, safe, convenient, reversible and almost user-independent method of birth control (12). After a deep gluteal or deltoid injection of 150 mg, contraceptive plasma levels are reached within 24 hours, and peak

plasma concentrations of 15-25 micrograms/ml are achieved within 20 days (12). Microcrystals are suspended in an aqueous solution that results in delayed absorption from the injection site and consequently prolongs the circulating concentration of the active progestin (12). Thus, effective plasma concentration for this birth control method is sustained for at least 14 weeks, and ovulation is suppressed, on the average, for 18 weeks (12).

DOCA is a highly selective gonane progestin that has been approved for use in the United States in a monophasic formulation containing 150 micrograms of desogestrel and 30 micrograms of ethinyl estradiol (13,14). Desogestrel was one of the three new progestational agents synthesized from levonorgestrel that were developed and brought into clinical trials during the late 1970s (13). Although new to the U.S. market, DOCA has been used for almost a decade and is the most widely prescribed oral contraceptive pill in Europe. The available literature on this new formulation demonstrates that this new preparation is effective and well tolerated by most women (13,14).

Although each of these new methods of contraception may have unique contraceptive and health benefits for servicewomen, data comparing outcomes are not available. To achieve the specific aim set forth in this proposal, we will compare these contraceptives on selected outcomes (method continuation, satisfaction, dysmenorrhea, menstrual bleeding, pregnancy prevention, bone density, and plasma lipid levels) believed to be most critical for women serving in the Armed Forces.

Contraceptive Continuation. Although the continuation rate of pill use is reported in contraceptive textbooks to be 75% after 12 months of use (7,15), this figure is misleading. Most likely, this rate is inflated because it is based on the responses of married women whose contraceptive practices may be more consistent than a more diverse group of sexually active

women (16,17). A more accurate estimate of pill continuation rates may be obtained by reviewing data from clinical trials that sample a more representative pool of women. Data from DOCA trials demonstrate that approximately 65% and 50% of women continued use of these pills for 12 and 24 months, respectively (18,19). Furthermore, these studies and others note that intermenstrual bleeding (breakthrough bleeding and spotting) is a common reason for pill discontinuation (13,14,18,19). Because decreased rates of intermenstrual bleeding have been reported with use of DOCA, higher rates of contraceptive continuation are believed to occur with this method as compared to more traditional birth control pills (13,14). Clinical trials conducted with DMPA suggest that continuation rates with this method are even higher (80% at 12 months and 68% at 24 months) than those observed with the traditional or newer forms of oral contraceptives, perhaps because it is easy to use or because it induces amenorrhea (12,20-26). To date, however, no study has directly compared continuation rates among these different methods of contraception. The present proposal will help fill this void by systematically examining rates of continuation among three different methods of hormonal contraception after 6-, 12-, and 24-months of use.

Method Satisfaction. Factors which may influence user satisfaction and lead to contraceptive discontinuation include menstrual irregularities, weight gain, nausea, headaches, mood changes, dizziness, acne, fatigue, and breast swelling or tenderness (7,27,28). Generally, discontinuation rates due to side-effects other than menstrual irregularities are less than 4%, but can vary according to method (27,29,30). One medical side effect of particular concern to many women is weight gain. Continuous weight gain has been associated with the progestin component of hormonal contraceptives (31). Double-blinded studies among different pill formulations suggest there is little evidence that oral contraceptive use leads to increased weight (29,30). In contrast,

DMPA use results in an average gain of 2-3 lb. per year (31). This side effect may be of particular concern to women serving in or planning to serve in the military, as those who gain weight secondary to contraceptive use may not meet the required weight/height physical standards unique to their branch of the armed forces after long term use. Although consistent exercise may help control this weight gain, a willingness to exercise may be impeded by DMPA use as preliminary studies suggest that this method results in increased fatigue (32).

Other issues that affect satisfaction relate to symptom improvement as a result of a particular hormonal method. For example, DOCA usually improves acne skin conditions among users. In one study of DOCA users, a significant proportion of women with acne reported complete resolution of this problem (13,14,19). Another benefit of oral contraceptives, especially DOCA, is the effect on hirsutism (13,14,19). Several studies employing this newly available oral contraceptive have reported significant improvement of this condition after 6 months of continued use. Unfortunately it is difficult to interpret data on method satisfaction from prior contraceptive studies because increased satisfaction with a method is usually inferred from a lack of reported medical side-effects by subjects, rather than by use of specific questions to inquire about satisfaction. For example, most women who participated in the multicenter clinical trials on DOCA reported excellent cycle control, reduced intermenstrual bleeding and spotting, and among women with dysmenorrhea, reduced symptomatology (13,19) Moreover, at 6-, 12-, and 24-months of use, about 88%, 92%, and 94%, respectively, of the sample did not report any medical side-effects (19). Thus, researchers concluded that a high degree of method satisfaction, and therefore continuation, existed for those women taking this newly formulated pill (13,14,19). Investigators of DMPA found that about 64% of women did not report any medical side-effects (and thus were satisfied) in any one year during a five-year follow-up evaluation (23).

Unfortunately, variations in study methodology have made it difficult to compare user satisfaction across studies and no single study has compared method satisfaction across different methods of contraception. This study will help fill this void by systematically evaluating method satisfaction including medical side-effects after 6-, 12-, and 24-months of use.

Dysmenorrhea. One of the single, largest causes of periodic absenteeism and decreased work productivity among young civilian women is dysmenorrhea (5-10). Pain with menstruation, or dysmenorrhea, represents a common gynecological complaint affecting approximately 70% of young women (5-10). Fifteen percent of young adult women who report pain with menstruation state that it is severe enough to limit usual activity even when analgesics are used (6). This disorder is commonly treated with combined oral contraceptive pills. However, 30% of women given traditionally formulated pills continued to experience moderate to severe dysmenorrhea (9). Studies of DOCA suggest that this new formulation may be more beneficial than traditional pills in ameliorating dysmenorrhea, perhaps due to a decrease in breakthrough bleeding episodes (19). For example, an open cross-over study on women with primary dysmenorrhea which did not respond to traditional pills noted that a significant number who used DOCA for 3 months reported reduced pain and 80% of the sample wished to remain on this pill formulation (10). Another study found that 50% of women taking DOCA reported significant improvements in their dysmenorrhea after using this formulation of one month (19).

Traditionally, the therapy for dysmenorrhea has been the oral contraceptive pill because it reduces the prostaglandin content of menstrual fluid and therefore decreases uterine motility (5-10). However, specific comparative studies examining treatment efficacy of various contraceptive regimens have not been conducted. Although the etiology of dysmenorrhea has yet to be clearly elucidated, it is suspected that the amelioration of dysmenorrheic symptoms is due

to the suppression of ovulation (9). Data collected from clinical DMPA trials has found that up to 70% of users are amenorrheic after 4 or more injections. Thus, if cessation of ovulation results in decreased symptoms, long-term use of DMPA may provide greater benefit than any pill formulation.

Menstrual Bleeding. All hormonal contraceptive methods affect the menstrual cycle and may influence the pattern and amount of bleeding (33). Contraceptives generally affect the menstrual cycle in one of 2 ways: (1) cyclic bleeding continues, as with oral contraceptive pills, where the hormonal formulation substitutes an artificial cycle for the woman's own cycle, but withdrawal bleeding occurs during the last 5-7 days; or (2) the normal cycle is partially or completely suppressed and the method does not induce cyclic bleeding, as with DMPA (33).

Irregular bleeding may also occur with use of hormonal contraception. However, the frequency of intermenstrual bleeding tends to decrease with continued use. Unfortunately, many clinical trials, especially those conducted 5 or more years ago, do not report their bleeding rates in a standard fashion, i.e., across 90-day reference periods (number of bleeding, spotting, and nonbleeding episodes that are summed across a 90-day period). Thus, data cannot be directly compared between formulations. Nonetheless, data collected on clinical trials of DOCA suggest a marked reduction in breakthrough bleeding (BTB) and spotting (14). Although BTB is more prevalent in the first few cycles of use (1.2-10%), by the sixth cycle, reported rates have decreased to 0.4-9.2% among users (14). With regard to spotting, rates are reported to decrease from 18.2% at cycle 1 to 5.8% by cycle 6 (14). In contrast, DMPA users commonly report episodes of unpredictable spotting and bleeding lasting seven or more days during the first few months of use. Data collected from an efficacy study found that the average number of bleeding or spotting days per 90-day reference period was 24.2 at 3 months, 18.5 at 6 months, 10.7 at 12

months, 7.6 at 18 months, and only 6.8 days at 24 months (26). However, as women continue with this hormonal method, amenorrhea becomes common. More than 70% of women develop this condition after 4 or more injections (12). This may be of particular benefit during periods of deployment. This study will directly compare the number of bleeding days associated with use of three different hormonal methods.

Pregnancy Prevention. Unplanned pregnancy among military servicewomen accounts for a significant number of hospital visits and loss of work productivity. As previously stated, pregnancy was the single largest cause of medical evacuation out of the theater during Operation Desert Shield/Storm (3). A longitudinal investigation of Navy women who enlisted between 1973 and 1987 found that for the first year of active-duty, the highest rates of hospitalization for the 1973-77 cohort was for induced abortion, while complications of pregnancy represented the highest hospitalization rate for the 1983-87 cohort (34). Moreover, pregnancy-related conditions continued to contribute to high levels of hospitalization for the remainder of this five-year active-duty interval. With the increase of female soldiers in combat areas, it will also be critical to protect personnel who are taken prisoner from becoming pregnant as a result of rape as recent conflicts demonstrate that this act is increasing as a crime of war (35).

Used consistently and correctly, the monophasic norethindrone oral contraceptive has a theoretical efficacy rate of 99% (27). However, the actual occurrence of pregnancy is as high as 8% due to poor daily compliance (36). Contraceptive management to ensure daily adherence is challenging because noncompliance may not be a willful, conscious act. More frequently, it is due to forgetfulness or misunderstanding of when to initiate pill use or what to do when a pill is missed (27,28). In contrast, DMPA is almost user-independent. A recent cost-benefit analysis conducted for pregnancy prevention compared DMPA with two different birth control pills and

Norplant® (37). These researchers reported that among pill users, the actual contraceptive efficacy was 95% versus 99.7% among DMPA users and concluded that DMPA delivered the highest net benefit for pregnancy prevention.

Bone Density The evaluation of hormonal effects on bone density are critical to the military, because a high incidence of musculoskeletal injuries, including stress fractures, have been reported among females in the eight weeks of basic training (38), and similar problems are likely to occur in combat situations. One particular concern with the use of DMPA by military women, therefore, is the suggestion that it may adversely affect bone density. A recent study examining bone density changes in women who had used DMPA for 5 or more years found reduced lumbar spine and femoral neck densities, compared to findings in premenopausal controls (39). However, these data are somewhat difficult to interpret because the study sample was considerably older (most in their mid-40s), and over half were smokers, factors that have been shown to contribute to loss in bone density.

In contrast, three cross-sectional studies and one longitudinal study have shown that NOCA favorably affects bone mass (40-42). For example, Lindsay et al (40) examined two groups of women aged 25 to 33 years who had variable health histories and found a 1% gain in bone density occurred for each year of pill use. DOCA has been associated with maintenance of bone mass in two separate studies (14,43). Ricci, Mango, Manna, et al. (43), examined the effects on bone mass density among 17 nulliparous women who had never taken oral contraceptives. These researchers found that bone density after one year of use was comparable to pretreatment levels. Another study employing a slightly different formulation (20 micrograms of ethinyl estradiol) conducted in Italy examined premenopausal women and reported a preservation of bone mass after two years of use (44). These authors conclude that DOCA does not appear to have any

deleterious effects on bone density, but does not offer any protective effects for fracture rates either. Thus, it appears that no harmful effects on bone density result from oral contraceptive use and in some premenopausal women using pills, positive effects may result.

Plasma Lipid Levels. A "perfect" hormonal method of birth control would neither increase plasma levels of total cholesterol and low density lipoprotein (LDL) nor reduce high-density lipoprotein cholesterol (HDL) (45). However, the estrogen component of traditionally formulated oral contraceptives usually raises HDL-cholesterol and triglycerides levels (18) while the progestin component has the opposite effect and tends to lower HDL-cholesterol (18). The importance of such changes in the genesis of arterial vascular disease in users of oral contraceptives is not clear, but presents some cause for concern (45). Although a definitive study examining these concerns has not been conducted, it is generally believed that plasma lipid level changes are likely related to the specific type and dose of progestin employed (7). For example, one study comparing two groups of women taking triphasic formulations (Ortho-Novum® 7/7/7 and Triphasil®) with non-contracepting controls found significant increases in total plasma cholesterol, LDL-cholesterol, and triglycerides levels after 6-months of use (45). Triglyceride levels declined by 12-months, but total- and LDL-cholesterol levels maintained these elevations at one year. HDL-cholesterol was not significantly different after 6- or 12-months of use. Although these researchers found statistically significant differences between women on pills compared to nonusers, all values were within acceptable clinical or normal ranges (45). Thus, the authors conclude that any contribution to increased atherogenesis by either formulation is highly unlikely.

A recent review of more than 50 clinical studies employing DOCA report that this new formulation did not interfere with estrogen's effects on lipoprotein metabolism (13). Although

data suggest that statistically significant increases in HDL-cholesterol were found, LDL-cholesterol remained unchanged or demonstrated a slight reduction (13). Another study examining nine groups of women using different oral contraceptives with non-contracepting controls found that levels of LDL-cholesterol were reduced by 14% in those taking pills containing desogestrel and by 12% in those taking low-dose norethindrone (44). Furthermore, these researchers found that the pills traditionally prescribed by the military (NOCA), which contain high-dose norethindrone, did not affect HDL-cholesterol levels, whereas those taking DOCA had increased their HDL by 12% (46). However, duration of oral contraceptive use in this study varied from 3-months to 4-years rendering specific conclusions difficult to interpret.

Conflicting findings on plasma lipid levels among DMPA users have been reported (12). In one study examining the long-term use (5-12 years) of several different contraceptive methods, DMPA caused a moderate decrease in triglycerides, HDL-cholesterol, and apoproteins, whereas estrogen-dominant pills (2 mg norethisterone, 0.1 mg mestranol) increased these same parameters (47). Some investigators have concluded that long-term use of this agent includes some change in lipid metabolism that would be considered a risk factor for atherosclerosis (48).

Technical Objectives

The broad aim of this proposal is to provide critical data on contraceptive outcomes that may be used to generate reproductive healthcare guidelines for servicewomen who have varying needs depending on their military assignment. To accomplish this goal, we are using a prospective, longitudinal design, to compare outcomes among three different methods of contraception (NOCA, DOCA, and DMPA) and are recruiting participants from both military and civilian sites. Use of a nonmilitary site allows us to collect data from women whose health status and reproductive needs are likely to mirror those of reservists and new recruits. Each contraceptive condition will be comprised of approximately 150 women aged 18 to 33 years: one half are being recruited from active-duty servicewomen from one of five military bases in San Antonio and receive their care at Wilford Hall Medical Center, San Antonio, Texas and the remaining half are solicited from women in the greater Galveston-Houston area and receive their at either UTMB's Maternal and Child Health clinic in Galveston, Texas, or a satellite clinic in Webster, Texas. All potential civilian women must meet entry standards for the Armed Forces. All study participants are being assessed after 3-, 6-, 12-, 18-, and 24 months of contraceptive use.

At follow-up visits, subjects complete standardized measures of dysmenorrhea, menstrual pain, medical side-effects and method satisfaction, and submit completed monthly menstrual calendars. Physical examinations are performed by a nurse practitioner or physician at entrance into the study and after 12- and 24-months of continuous contraceptive use. In addition, bone density measurements (lumbar spine and femoral neck) using dual x-ray absorptiometry (DEXA) are obtained at baseline and the 24-month assessment, while lipid levels are being assessed at baseline and after 12- and 24-months of contraceptive use. DMPA participants return to the

clinic at 9, 15, and 21 months to receive an injection only. The specific technical objectives of this study are to determine, at the conclusion of 2 years, which of these three methods:

1. has the highest rate of continuation;
2. has the highest level of user satisfaction;
3. most effectively reduces the occurrence and severity of dysmenorrhea;
4. most effectively decreases the number of bleeding days per 90-day reference period;
5. has the lowest user failure rate resulting in pregnancy;
6. minimizes bone density loss;
7. minimizes changes in lipoprotein levels; and
8. minimizes the occurrence medical side-effects.

Data will be analyzed employing repeated measures multivariate statistical tests so that (1) trends in outcomes over 24 months of contraceptive use can be examined; (2) comparisons of outcomes at specific points in time (6, 12, and 24 months) may be performed; and (3) main effects for method, time, recruitment site, and their interactions can be evaluated. The results of these analyses will help determine the safest, most convenient, and most effective contraception for servicewomen in various phases of duty, i.e., deployed and nondeployed. For example, women who are deployed for two years may experience more contraceptive and noncontraceptive benefits (few bleeding days) as well as greater long-term satisfaction with an injectable contraceptive as compared to an oral contraceptive. In contrast, non-deployed servicewomen with severe dysmenorrhea may experience the greatest relief from DOCA, and hence have reduced absenteeism.

Body

This third summary report details the specific activities that have occurred during Year 3 of funding (September 23, 1998 through September 22, 1999). According to our Statement of Work, there are a total of 5 major objectives. All tasks in Objective 1 were initiated and completed during the first 24 months of the granting period. Thus, four major objectives and related tasks were to be completed during the third 12 months of funding. Objectives two through five are to establish the three cohorts each consisting of 150 participants; complete required medical assessments, laboratory tests, and self-report and satisfaction measures at each visit; analyze preliminary study data and complete the yearly annual report. The progress on each objective is addressed in this report.

Objective 2: Establish the three contraceptive cohorts (users of norethindrone-containing pills, desogestrel –containing pills, and DMPA).

Although this objective and related task were to be completed in year 2, as mentioned in last year's summary report recruitment of subjects at both UTMB and WHMC was more difficult than forecasted. However, we are pleased to report that all six tasks in this objective have been completed. These include: 1) recruit and obtain informed, written consent from all study participants; 2) insure that each ethnic population is adequately represented at UTMB; 3) complete the initial medical examination and history; 4) complete initial self-report measures for all participants and disseminate instructions for completing menstrual calendars; 5) collect and conduct data entry of demographic data required for subject tracking; and 6) complete recruitment of all participants into one of the three contraceptive conditions.

Task 1. *Recruit and obtain informed, written consent from all study participants.* As mentioned in our year 2 summary, we originally projected enrollment to be 225 at both sites by

30 September 1998. However, with the permission of the Scientific Officer, Dr. Patricia Mudrow, recruitment into this study ceased on 2 December, 1998 at both sites. We have enrolled 203 women at UTMB and 183 active duty women WHMC resulting in a cohort of 386 (see table below). Written informed consent has been obtained from all subjects.

Table 1. Enrollment by contraceptive condition and site.

Contraceptive	**UTMB**	**WHMC**
Depo-Provera	76	61
Ortho-Novum 1/35	59	60
OrthoCept	68	62

Task 2. *Insure that each ethnic population is adequately represented in the study cohort.* Currently 72.5% of our entire cohort is Caucasian, 16.3% African-American, and 9.1% Mexican-American. Approximately 2.1% percent of subjects report a race/ethnicity other than Caucasian, African-American, or Mexican-American. Although this represents fewer African-Americans (31% African-American) than the number in the military, all three racial groups are represented in our cohort.

Task 3. *Complete the initial medical examination and history.* All recruited subjects have completed an initial medical examination and provided a thorough history, including past contraceptive practices and menstrual history. Each subject was screened for pregnancy and other potential health risks that would preclude the use of hormonal contraception.

Task 4. *Complete initial self-report measures for all participants and disseminate instructions for completing menstrual calendars.* All recruited subjects have completed their self-report measures and have received instructions for completing menstrual calendars. The self-report questionnaires take 30–45 minutes to complete. All forms are reviewed by project

personnel while the patient is still at the clinic so that missing or inconsistent information can be addressed.

Task 5. *Collect and conduct data entry of demographic data required for subject tracking.* Electronic databases that were developed in year 1 continue to be used to: 1) monitor recruitment (eligibility and recruitment strategies used), 2) track subjects (demographics and appointments) and, 3) measure contraceptive discontinuation rates. These databases contain the necessary information to successfully contact subjects about future appointments, as well as to monitor the race/ethnicity distribution of the sample and the contraceptive conditions selected, and to determine the success of various recruitment efforts. All databases are linked to a mechanism for automatic data monitoring that provide a hard copy of results, as needed.

Task 6. *Complete recruitment of all participants into one of the three contraceptive conditions.* As mentioned previously, recruitment was completed on 2 December 1998. From September 23, 1998 – December 2, 1998, 42 subjects were enrolled in the study.

Objective 3: Complete required follow-up medical assessments, laboratory tests, and self-report and satisfaction measures at each visit.

Activities associated with this objective are designed to maintain the research cohort. Ten tasks are associated with achieving this objective and include: 1) order, prepare, and Xerox required study forms as well as appointment reminder post cards; 2) prepare and mail appointment reminder postcards to each participant; 3) perform tracking procedures on participants whose appointment reminder cards were returned undelivered; 4) compensate UTMB subjects for their participation in the study at each follow-up visit and contact via phone all discontinuers; 5) dispense oral contraceptives or administer Depo-Provera and count unused

or missed birth control pills; 6) complete brief medical visit and satisfaction/side-effect measures at the 3-month follow-up visit; 7) complete brief medical visit and satisfaction/side-effect measures at the 6-month follow-up visit; 8) complete yearly medical visit including satisfaction/side-effect measures, and blood tests; 9) complete brief medical visit and satisfaction/side-effect measures at the 18-month follow-up visit; and 10) complete final visit which includes satisfaction and side-effect measures, well-women examination, laboratory tests, and bone density scan. Each of these tasks has been accomplished.

Task 1. *Order, prepare, and Xerox required study forms as well as appointment reminder post cards.* A system has been established to electronically monitor all follow-up visits and create reminder letters.

Task 2. *Prepare and mail appointment reminder cards to each participant.* At the conclusion of each subject's initial visit, she is provided with an appointment for her next follow-up visit. A reminder letter is generated from our electronic database 14 days prior to her appointment. Each subject is also called one day before her scheduled appointment as a reminder.

Task 3. *Perform tracking procedures on participants whose appointment reminder cards were returned undeliverable.* At this time, 25 reminder letters have been returned as undeliverable. In these cases, tracking procedures by phone were implemented. Using this technique, we have been able to maintain contact with all but 4 subjects who missed their scheduled follow-up appointments. We are in the process of obtaining correct mailing addresses on these individuals.

Task 4. *Compensate UTMB subjects for their participation in the study at each follow-up visit and contact via phone all discontinuers..* All subjects at UTMB who have returned for

follow-up visits have received compensation each visit. Subjects recruited at WHMC cannot receive compensation per installation policy. At this time, 105 subjects at UTMB and 98 subjects at WHMC elected to discontinue their chosen contraceptive method. Of these, 198 subjects have been successfully contacted at regular intervals by phone or mail to complete the discontinuation assessment. Multiple attempts to reach the remaining 5 subjects by phone, mail, or through family or friends have been unsuccessful to date.

Task 5. *Dispense oral contraceptives or administer Depo-Provera and count unused or missed birth control pills.* At the initial visit, all women assigned to either pill condition receive a four month supply of pills, and are told to initiate use the Sunday after the start of their period. At the 3-month follow-up visit, another 3 pill packs are provided. During the reminder phone call about appointment time, pill users are also asked to bring in their pill packs. Each pill package has been numbered with the month it is to be used, and counts of all missed pills are recorded on the Nursing Assessment scannable form. With regard to Depo-Provera users, subjects have returned to the clinic to receive their injection after the start of their period. These subjects are scheduled for an injection 90 days after their initial injection. To date, all subjects using this birth control method have received their follow-up injection within 2 weeks of their scheduled appointment.

Task 6. *Complete brief medical visit and satisfaction/side effect measures at the 3-month follow-up visit.* At this time, all subjects who continued with their contraceptive method have completed their 3-month follow-up visit. During this visit, each subject was interviewed to determine whether any medical problems had been encountered during this period. A structured interview using a scannable form was developed to accurately evaluate the occurrence and

resolution of common medical side effects. This is completed by the medical provider at each visit. All subjects then completed the remaining self-report measures prior to leaving clinic.

Task 7. *Complete brief medical visit and satisfaction/side effect measures at the 6-month follow-up visit.* All subjects who continued with their chosen contraceptive method have also completed their 6-month follow-up visit at both UTMB and WHMC. Each subject was interviewed to determine whether any medical problems have been encountered from month 3 through month 6. A structured interview using a scannable form was developed to accurately evaluate the occurrence and resolution of common medical side-effects. This is completed by the medical provider at each visit. All subjects then completed the remaining self-report measures prior to leaving clinic.

Task 8. *Complete yearly medical visit including satisfaction/side effect measures, and blood tests.* All subjects who attended their 12-month follow-up completed a well-women exam, including general physical examination with pap smear and blood work for Cardiac Risk Panel and Coulter Profile. Cultures for sexually transmitted disease were taken routinely at UTMB as standard of care. WHMC performs STD cultures only if indicated. Subjects also completed the self-report measures of satisfaction, dysmenorrhea, and medical side-effects. In addition, menstrual calendars were reviewed and the number of missed pills counted by the medical provider.

Task 9. *Complete brief medical visit and satisfaction/side effect measures at the 18-month follow-up visit.* To date, 86 subjects have completed the 18-month visit. At this visit, the self-report measures of satisfaction, dsymenorrhea, and medical side effects were completed. In addition, menstrual calendars were reviewed and the number of missed pills counted by the medical provider.

Task 10. *Complete final visit which includes satisfaction and side-effect measures, well-woman examination, laboratory tests, and bone density scan.* . To date, 28 subjects have completed the final visit. All subjects who completed this visit underwent a well-woman examination which includes a general physical exam with Pap smear. In addition, blood was obtained for a Cardiac Risk Panel and Coulter Profile. Cultures for sexually transmitted disease were taken routinely at UTMB as standard of care. WHMC performs STD cultures only if indicated. Subjects also completed self-report measures of satisfaction, dysmenorrhea, and medical side effects. In addition, menstrual calendars were reviewed and the number of missed pills counted by the medical provider. Table 2 below outlines the number of medical visits by follow-up date for both UTMB and WHMC as of 19 October 1999.

Table 2. Follow-up medical visits completed by site.

Visit Type	UTMB	WHMC
3-month	171	148
6-month	144	118
12-month	107	84
18-month	53	33
24-month	20	8

Objective 4: Analyze study data

This objective involves quantifying study results. There were 5 tasks identified for this objective relevant to year 3: 1) conduct reliability analysis on 10% of medical visits; 2) perform all data entry and verification of study data; 3) reconcile out-of range and inconsistent data elements to insure accuracy of study data; 4) perform preliminary analyses; and 5) presentation of preliminary findings.

Task 1. *Conduct reliability analysis on 10% of medical visits.* Audiotaping of 10% of the visits at each site is completed to insure that provider/patient interaction is the same for both sites. To date, audiotapes of 127 (10% of visits) visits have been completed and reviewed. Analyses of the data indicate that standardization of visit interaction across sites is excellent at 92.5% accuracy.

Task 2. *Perform all data entry and verification of study data.* Software programs to electronically scan computer ready questionnaires of the four self-report measures has been completed. Thus, data entry is all electronic. Data entry and verification has been completed for all data collected at the initial visit. Scanning of questionnaires is being completed for all the 3, and 6-month visits.

Task 3. *Reconcile out-of-range and inconsistent data elements to insure accuracy of study data.* All forms are being visually inspected after completion to insure accuracy of collected data. Out of-range evaluations are conducted at the time the visit-specific databases (initial, 3-month, 6-month, 12-month, 18-month, and 24-month) are being assembled. Out of range evaluation has been completed on the initial and 3-month databases. The 6-month database has been electronically scanned and cleaning has begun.

Task 4. *Perform preliminary analyses.* Analysis of baseline data is underway. Descriptive characteristics of the whole sample and by site are included in the following tables.

Table 3. Demographic characteristics

	Both sites		UTMB		WHMC		p
Age @ study initiation (y)							
Mean	24.2 ± 4.0		24.3 ± 4.1		23.9 ± 3.9		.314
Range	18-33		18- 33		18-33		
Weight (lbs.)							
Mean	135.9±4.0		135.4±21.07		136.62±17.3		.546
Range	96-192		96-192		99-184		
Gravidity							
0	187	(48.4%)	99	(48.8%)	88	(48.1%)	
1	97	(25.1%)	45	(22.2%)	52	(28.4%)	
2	56	(14.5%)	29	(14.3%)	27	(14.8%)	
3	27	(7.0%)	18	(8.3%)	9	(4.9%)	
4 or more	19	(4.9%)	12	(5.9%)	7	(3.8%)	
Parity							
0	245	(63.5%)	125	(61.6%)	120	(65.6%)	
1	83	(21.5%)	47	(23.2%)	36	(19.7%)	
2	45	(11.7%)	22	(10.8%)	23	(12.6%)	
3	11	(2.8%)	7	(3.4%)	4	(2.2%)	
4 or more	2	(0.5%)	2	(1.0%)			
Elective abortions							
0	295	(76.4%)	152	(74.9%)	143	(78.1%)	
1	67	(17.4%)	37	(18.2%)	30	(16.4%)	
2	21	(5.4%)	12	(5.9%)	2	(4.9%)	
3	1	(0.3%)	1	(0.5%)	0		
4 or more	0		0		0		
Spontaneous abortions							
0	349	(90.4%)	181	(89.2%)	168	(91.8%)	
1	32	(8.3%)	19	(9.4%)	13	(7.1%)	
2	3	(0.8%)	2	(1.0%)	1	(0.5%)	
3	2	(0.5%)	1	(0.5%)	1	(0.5%)	
4	0				0		
Are you married?							
Yes	117	(30.3%)	146	(71.9%)	60	(32.8%)	.298
No	268	(69.4%)	57	(28.1%)	122	(66.7%)	
Not married but has a partner	198	(1.3%)	113	(55.7%)	85	(46.4%)	.125
Ever smoked cigarettes	206	(53.4%)	114	(56.2%)	92	(50.3%)	

Table 4. Reproductive Characteristics.

	Both sites		UTMB		WHMC		p
Ever taken birth control pills							
Yes	323	(83.7%)	170	(83.7%)	153	(83.6%)	.932
No	62	(16.1%)	33	(16.3%)	29	(15.8%)	
Seen doctor for painful menses							
Yes	110	(28.5%)	56	(27.6%)	54	(29.5%)	.742
Been absent from work due to painful menses							
Yes	97	(25.1%)	62	(30.5%)	35	(19.1%)	
Age at first menses (y)							
Mean	12.7 ± 1.5		12.7 ± 1.5		12.7 ± 1.5		.636
Range	8-17		8-17		8-17		
Age first started taking pill (y)							
Mean	18.3 ± 4.7		18.1± 5.9		18.0 ± 2.7		.871
Range	11-30		13-30		11-29		
Age subject first delivered a child (y)							
Mean	21.7 ± 3.5		21.5 ± 4.1		21.8 ± 2.7		.606
Range	14-32		14-31		16-32		

Table 5. Laboratory results at baseline.

	Both sites	UTMB	WHMC	p
Systolic blood pressure (mm/Hg)				
Mean	119.7 ± 78.8	122.8 ± 108.2	116.3 ± 10.8	.000
Range	69-147	69-140	82-147	
Diastolic blood pressure (mm/Hg)				
Mean	67.5 ± 9.2	70.6 ± 7.7	64.1 ± 9.5	.000
Range	41-90	48-90	41-88	
Total cholesterol (mg/dL)				
Mean	190.4 ± 115.0	189.6 ± 105.3	191.2 ± 125.1	.211
Range	84-292	84-285	103-292	
HDL cholesterol (mg/dL)				
Mean	57.8 ± 14.5	59.3 ± 15.9	56.0 ± 12.6	.031
Range	28-149	28-149	29-112	
LDL cholesterol (mg/dL)				
Mean	98.6 ± 29.5	98.2 ± 28.5	99.1 ± 30.74	.760
Range	27-218	27-210	28-218	
HGB (g/dl)				
Mean	13.4 ± 1.1	13.5 ± 1.3	13.3 ± 0.9	.122
Range	9.20-23.30	9.20-23.30	9.30-16.30	
HCT (%)				
Mean	39.6 ± 2.8	40.0 ± 2.9	39.19 ± 2.6	.003
Range	26.90-50.10	29.90-50.10	26.90-47.20	
Density of lumbar spine (DEXA)	1.08 ± 0.1	1.03 ± 0.1	1.16 ± 0.1	

Table 6. Discontinuation at 3 and 6 months.

	Both sites	UTMB	WHMC	p
3 months	67 (17%)	32 (16%)	35 (19%)	.384
6 months	124 (32%)	59 (29%)	65 (36%)	.175

Task 5. *Presentation of preliminary findings.* Analyses of follow-up data will be initiated when all subjects have completed their 12 month visit. Presentation of data will begin in Year 4.

Key Research Accomplishments

During this third year of funding, we have accomplished the following tasks:

- Completed recruitment of final cohort
- Completed initial visit on all subjects, including history and physical examination, completion of self-assessments, and collection of blood samples
- Completed 3 and 6 month follow-up visits on all subjects
- Calculated discontinuation rates by site at 3 and 6 months
- Completed follow-up visits at 12, 18, and 24 months on 191, 86, and 28 subjects respectively
- Completed audiotaping of research team interactions with patients of 10% of all visits at both sites
- Completed analyses of audiotapes to determine reliability between sites
- Completed data entry, verification and cleaning of all baseline data
- Compared comparison of demographic and reproductive characteristics at baseline by site
- Compared comparison of baseline laboratory values by site

Reportable Outcomes

During Year 3, we obtained additional funding based on work supported by this grant. On September 1, 1999, the National Osteoporosis Foundation awarded the PI with a grant of $40,000 to augment our work on the relationship between hormonal contraception and bone mineral density. Funding from the Department of Defense will allow us to investigate bone mineral density changes after 24 months of contraceptive use. Funding from the National Osteoporosis Foundation will be used to investigate bone mineral density changes after only 12

months of contraceptive use and to measure changes in bone mineral density among women using non-hormonal contraception at baseline and 12 months. This additional funding will provide valuable new information on changes in bone mineral density among military and civilian women who use contraception.

Conclusion

During year 3 of funding, we completed the recruitment of subjects at both sites. We recruited 203 subjects at UTMB and 183 at WHMC; thus, a total of 386 women have completed their initial medical visits. Further, all women who have continued with their chosen method of contraception have completed their 3- and 6- month follow-up visits. Audiotaping of visits demonstrates that the reliability to date between the two sites is excellent. Scanning and analyses of baseline data were completed during Year 3 as well. During Year 4, follow-up data will be analyzed by contraceptive condition and preliminary findings will be submitted for presentation.

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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 1 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession document numbers be changed to "Approved for public release; distribution unlimited." Copies of these reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLLIS M. RINEHART
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