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Highly trained female athletes may experience loss of menses, low bone mass, and an increased frequency of stress fractures because of their participation in intense physical activity. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fractures. This study is a two-year randomized trial of the effects of oral contraceptives on bone mass and stress fracture incidence among 150 female competitive cross country runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass in being measured at five sites: Massachusetts General Hospital, University of California Los Angeles, University of Michigan, Stanford University/Palo Alto VA Medical Center, and Helen Hayes Hospital in West Haverstraw NY. Athletes are currently being recruited from the areas around these five clinical sites, and to date 35 have been randomized. We are awaiting IRB approval to enter several others into the trial. Results will not be available until 2002.

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FOREWORD

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Jennifer J. Kilroy 10/20/99

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(5) INTRODUCTION

Highly trained female athletes may experience loss of menses because of their participation in intense physical activity. Previous cross-sectional research has shown that women with exercise-induced irregularities have a significantly higher frequency of stress fractures and low bone mass than normally menstruating controls. Longitudinal studies suggest that these women are losing bone mass over time. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fracture. This study is a two-year randomized trial of the effect of oral contraceptives on bone mass and stress fracture incidence among 150 female cross country runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass is being measured at five sites: the Massachusetts General Hospital, the University of California Los Angeles, the University of Michigan, Stanford University/Palo Alto VA Medical Center, and the Helen Hayes Hospital in West Haverstraw, NY. Athletes are being recruited from the areas around these five clinical sites.

(6) BODY

At the outset, it is useful to summarize the progress of the first year by stating that a great deal has been accomplished, but recruitment has been much more difficult than anticipated. Below we summarize (a) the progress that has been made, (b) the current status of recruitment, (c) our plans for reaching our goal of 150 athletes this winter, and (d) the results of some very preliminary statistical analyses.

(a) Progress (excluding recruitment, which will be described under [b] below): Among the accomplishments are the following: The study has been introduced to coaches, athletes, student health services, and IRBs at many colleges, and procedures have been implemented to work with these individuals and groups. Informational packets have been developed and sent to coaches, athletes, student health services, and others. Informed consent forms have been developed and administered. Annual questionnaires, daily diaries, and six-month questionnaires have been developed, pilot tested, and, in the case of the baseline questionnaire and daily diaries, used for data collection. Date entry programs have been written and successfully used. A manual for the clinical sites has been written and implemented. The Project Director (Kristin Cobb) has spoken to athletes at many colleges and recently has begun to make the study known to athletes at high-profile races in the Stanford area. A randomization scheme has been developed and implemented. Oral contraceptives have been procured from Wyeth-Ayerst and procedures established for sending them to student health services and tracking them. Procedures have been set up with the study's medical monitor. Preliminary statistical analysis of the baseline data has been undertaken on the first 25 participants. Of all these tasks, by far the most time has been spent on working with so many different IRBs (many of which meet only a few times a year) and on recruitment.

(b) Recruitment: Initially, recruitment was to take place around three bone densitometry sites in Boston, Ann Arbor, and Los Angeles. Soon the Stanford-affiliated Palo Alto VA Medical Center was added as a fourth site, and recently the Helen Hayes Hospital in West

Haverstraw NY was added as a fifth site. We are awaiting army IRB approval to begin seeing runners at the Helen Hayes Hospital.

Ms. Cobb has contacted and sent an informational packet to cross country coaches at 94 colleges in the areas around Boston, Ann Arbor, Stanford, Los Angeles, and New York. She has given talks to 51 teams. The first recruiting trip was made in late summer 1998, the second in the spring of 1999, and the third in the fall of 1999. Of the 43 teams not visited, 2 talks are still pending, 15 coaches did not want their athletes to participate, 9 administrations told us we could not speak at their schools even though the coaches were supportive, and 17 talks did not work out because of scheduling difficulties or adverse weather. Of the 51 teams that were spoken to, 18 schools have full approval, 19 schools are awaiting either student health service or IRB approval, 7 IRBs denied approval, and 7 did not have eligible and/or interested athletes.

Six hundred eleven athletes have attended these talks to date. So far, 385 of these were sent e-mail invitations to participate in the study. (We did not obtain IRB approval or IRB approval is pending for the other 226 athletes.) Eighty-seven of the invited athletes responded that they were interested in participating, and, following preliminary screening for eligibility by Ms. Cobb, 72 appeared to be eligible. Eighteen of these, however, decided they did not want to be in the study after all. Of the others, 37 have visited their student health service to be checked for medical contraindications to oral contraceptives, 35 were found by the health service to be medically eligible, and 30 have been randomized. When it became apparent that recruitment from the college teams was more difficult than anticipated, the criteria for enrollment were expanded to include students at the same colleges who were not on college teams but who run at least 40

miles per week and who have participated in at least 5 competitive races in the past year. Nineteen additional potential participants were found through advertisements in school newspapers, postings, advertisements at road races, and advertisements in running club newspapers. Of these 19 were screened by Ms. Cobb, 19 were found to be eligible by her, 7 have visited the student health services, 5 were found to be medically eligible by the student health service, and 5 have been randomized. Thus, to date a total of 35 runners have been randomized, starting in March 1999. An additional 29 students said they would enter the study this fall after exams and summer vacation, but we have now realized that most of these in fact have no intention of participating, and that only about 5 will. In addition, 7 runners recruited from the trip last Spring are ready to be seen by their health services, and within the last two weeks we have received approval from their college IRBs to enter them into the study. Thus, we anticipate that last year's recruitment efforts have yielded about 47 participants.

(c) Further recruitment efforts to reach our goal of 150 athletes:

(1) Pending army IRB approval of the protocol and consent form from the Helen Hayes Hospital, athletes will be enrolled from this area, which includes colleges in New York, New Jersey, and eastern Pennsylvania. In late August and early September, 1999, Ms. Cobb visited this area and talked to 13 cross-country teams. In addition, two teams were sent brochures when talks were cancelled because of Hurricane Floyd. Advertisements will be placed to recruit other eligible students at the 15 colleges. Ms. Cobb will also be giving talks at one other Stanford-area school (San Jose State) and one LA-area school (UC Irvine).

Judging from past experience, if each of these 17 schools provides 3 athletes, 51 more runners will be recruited in this way.

(2) At the 15 colleges where athletes started enrolling last year, packets have been mailed to coaches to give to freshmen. Since most freshmen are not already on oral contraceptives, we expect a relatively high proportion of these athletes at least to be eligible. So far, 11 freshmen from 6 teams have expressed interest and are currently being screened, and we estimate that 8 will enroll in the study.

(3) We have recently expanded our recruitment efforts to include non-student athletes who are in the age range 18-25 years, who run at least 40 miles per week, who have participated in 5 competitive races in the previous year, and who live in the areas around Stanford. Los Angeles, or New York City. We are awaiting army IRB approval to begin to enter runners into the trial in the Stanford and New York areas, and later will be seeking approval to expand this to the Los Angeles site. To date, 5 runners from the Stanford area have been screened by Ms. Cobb and 6 others have expressed interest and are awaiting preliminary screening. When we receive army IRB clearance, we will enroll them in the study. Our study has had a booth at some road races. In addition, lists are posted on the internet of participants in several road races that provide name, time, gender, and age of participants, so that if we can find their phone numbers we can invite them to participate in the study if they meet the eligibility criteria. We expect that, once we have approval from the various IRBs to enter runners into the study recruited in these ways in Stanford, Los Angeles, and New York, within 2-3 months we will have an additional 30 randomized participants. Because these

runners are not subject to NCAA regulations, we can pay them a small amount for their participation.

(4) Our Project Officer Lieutenant Colonel Sheehan has kindly offered to contact military populations such as West Point to augment our numbers further.

In summary, if we are able to recruit 51 athletes from the New York area schools and 2 additional California schools, 8 entering freshmen from the "currently active" schools, and 30 who are not students, then we would have a total of 89 additional participants, when we need 103 to join the 47 we now have. We hope that the addition of military populations will enable us to meet our goal of 150 runners.

(d) Preliminary statistical analyses:

Based on data from the baseline questionnaires and bone mass measurements on the first 25 participants, we found three factors to be statistically significantly associated with low bone mineral density in the spine: infrequent menstrual periods, current miles run per week, and weight.

(7) KEY RESEARCH ACCOMPLISHMENTS: None to date.

(8) REPORTABLE OUTCOMES: None to date.

(9) CONCLUSIONS: We will have no conclusions to report until the end of the trial.

(10) REFERENCES: None

(11) APPENDICES: None