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Evaluating the Effectiveness of Barrier Contraceptive Methods: Impact of Emergency Contraception

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Family Health International

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Acknowledgments
This meeting resulted from the collaborative planning of the committee members shown below. We wish to acknowledge the work of others who made this meeting possible. The morning presentations helped establish a common base of knowledge for the day's discussions. In addition to presentations by several members of the planning team, we appreciate presentations prepared by: Colin Pollard of the U.S. Food and Drug Administration, Felicia Stewart of the Henry J. Kaiser Family Foundation, Terri Walsh of the California Family Health Council, Tim Farley of the World Health Organization, and Markus Steiner of Family Health International (FHI). In addition, we appreciate the contributions made by all of the participants during the afternoon discussions, moderated by FHI President Willard Cates, Jr. This was truly a participatory meeting, and without the contributions made by all of the participants, we would not have achieved our purpose. Finally, we thank the U.S. Agency for International Development for supporting the cost of the meeting.

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Executive Summary

The methodologies of clinical trials that evaluate barrier contraceptives need to be examined because of the growing availability of emergency contraception (EC). Emergency contraceptive pills can provide an effective backup after a barrier method malfunctions or when a barrier method is not used during intercourse. This availability of EC complicates the process for determining the effectiveness of a barrier method in a clinical trial. Because of these issues, FHI organized a dialogue among a group of contraceptive researchers and regulators with two primary goals:

1. To review and clarify the study design, implementation and analysis complexities that arise when barrier methods are evaluated in a setting where EC is available.

2. To define better our research agenda with respect to determining the effectiveness of new barrier contraceptive methods.

The morning session was designed to lay a common foundation for the afternoon discussions. Presentations reviewed current understandings about the effectiveness of barrier methods and current U.S. Food and Drug Administration (FDA) thinking on communicating effectiveness to consumers through product labeling. Next came a summary of the availability and utilization of emergency contraception. Five presentations followed, with each focusing on experiences from recent or ongoing barrier contraceptive effectiveness trials. The last presentation of the morning summarized the types of questions that the afternoon discussion would address.

The afternoon discussion focused on five general questions about barrier contraceptive trials:

1. What do we want to know about the effectiveness of barrier contraceptives?

2. Should EC be provided in advance or upon request?

3. How should researchers calculate study results?

4. How do the studies affect product labeling?

5. Is the true efficacy study a viable option for consideration?

The group appeared to reach consensus on these points:

- A measurement of the effectiveness of the barrier method alone is needed.
- EC should be provided if a woman requests it, even if she said at the beginning of a trial she would not use it.
- The true efficacy approach holds promise, although more work is needed.

The group did not reach consensus on many other questions, notably: whether to provide EC in advance or upon request during a clinical trial, how meaningful EC-adjusted estimates of effectiveness would be, and how these estimates would affect product labeling.

More than 60 people participated in the meeting, including representatives from the U.S. Agency for International Development, the FDA, the National Institutes of Health, research organizations, individual investigators, the private sector and women's groups. ❖

Context for Discussing Barrier Methods and Emergency Contraception

The morning session included three presentations providing background information pertinent to discussing barrier methods and emergency contraception.

Effectiveness of Available Barrier Methods

— *Dr. James Trussell, Princeton University*

Four pieces of information about contraceptive effectiveness would help couples to make an informed decision when choosing a contraceptive method.

- *Failure rates during typical use* show how effective the different methods are during actual use (including inconsistent or incorrect use).
- *Failure rates during perfect use* show how effective methods can be, where perfect use is defined as following the directions for use — correctly using the method at every act of intercourse.
- *Failure rates during imperfect use* show how effective methods will be if they are used incorrectly or inconsistently.
- *The percentage of perfect users*, or percentage of months during which a method is used perfectly, reveals how hard it is to use a method correctly and consistently.

The difference between failure rates during imperfect use and failure rates during perfect use reveals how forgiving of imperfect use a method is. The difference between failure rates during typical use and failure rates during perfect use reveals the consequences of imperfect use. This difference depends both on how unforgiving of imperfect use a method is and on how hard it is to use that method perfectly.

Many investigators have recognized the importance of distinguishing between contraceptive failure associated with user error and failure attributable to the inherent inadequacy of the method itself. By convention, all failures that occur during a month (or menstrual cycle) in which a barrier method is either not used at every act of intercourse or used improperly are labeled user failures. Only those pregnancies that occur during a month (cycle) during which a method is used perfectly are classified as method failures; *perfect use* does not imply that the method did not fail, only that the method was used consistently and correctly according to a well-specified set of rules.

The standard procedure is to compute separate *method* and *user* failure rates (pregnancies divided by exposure). In this procedure, all exposure from *both* perfect *and* imperfect use is included in the denominator of both method and user failure rates. Under this convention, method and user failures are treated as two of many possible *causes* of method discontinuation. The sum of all cause-specific discontinuation rates is the overall or total discontinuation rate, and the sum of method and user failure rates is the overall or total failure rate. The common misinterpretation is that the resulting

method rate yields information about the inherent efficacy of the method. That this interpretation is incorrect is obvious when one realizes that inherent method efficacy can be measured only when the numerator (method failures) is assessed in relation to the proper risk set (exposure only when the method is used perfectly). Method failure rates computed by the standard procedure confound inherent method efficacy with the proportion of exposure that is characterized by perfect use.

There are two primary measures of contraceptive failure: the Pearl index pregnancy rate and life-table probabilities of pregnancy. The Pearl index is the ratio of the number of pregnancies observed in a study divided by the total number of years that all study participants have been exposed to the risk of pregnancy. A shortcoming of the Pearl rates is that they decline as the length of a study increases because participants likely to become pregnant tend to do so early, leaving in the study a pool increasingly comprised of more consistent and correct users or less fecund couples. With life table approaches, separate pregnancy rates are calculated for each month and then combined to yield the cumulative proportion of women becoming pregnant within specific time durations (e.g., 6 or 12 months).

Summaries of the best available estimates of the probability of becoming pregnant within the first year of typical use and of perfect use of each method can be found in Table 31-1 in *Contraceptive Technology* (Hatcher et al.). Tables 31-2 through 31-16 in the same publication summarize research results published separately for each method.

Uniform Contraceptive Labeling — An FDA Update

— *Colin Pollard, Chief, OB-GYN Devices Branch, U.S. Food and Drug Administration (FDA)*

Following approval of the female condom in 1992, the FDA initiated an effort to make labeling for all contraceptive products, both devices and drugs, use uniform language to convey information about protection from sexually transmitted diseases (STDs), as well as protection from pregnancy. In 1993, the FDA issued letters to manufacturers of all contraceptive products about how to label those products for STD protection:

STD Protection

— latex condoms for men (if used properly and consistently)

Equivocal/Difficult-to-Convey Message

Several contraceptive products require special labeling statements to address and position the product with respect to STD protection:

— natural skin condoms
— new material condoms, e.g., polyurethane
— female condoms
— diaphragms, caps, and spermicides

No Protection

— intrauterine devices (IUDs)

— tubal occlusion devices (TODs), e.g., Falope-Ring, Hulka Clip, Filshie Clip

— hormonal methods, e.g., oral contraceptives, Norplant, Depo-Provera

Between 1994 and 1996, the FDA also conducted a series of focus studies to develop a table that gives the effectiveness

of all contraceptive products and methods, including devices and drugs, in a form that is easy for the consumer to read and understand. This table is based on one that is published periodically in *Contraceptive Technology*. The industry has been asked to incorporate this table into their consumer labeling for their respective products. Health providers and educators are also encouraged to use this table when discussing contraceptive options.

The FDA will continue to update this table and its recommendations as new information becomes available. The influence of emergency contraception may affect contraceptive labeling at some point in the future. The FDA looks to researchers and others for ideas on how to keep these recommendations up-to-date and as meaningful to the consumer as possible.

Guidance on the FDA's uniform contraceptive labeling initiative was issued in July 1998 and can be accessed via the FDA's Web site, *http://www.fda.gov/cdrh/ode/contrlab.html*. Comments and suggestions about the FDA's uniform contraceptive labeling initiative may be submitted to Mr. Pollard (see the conference participants list for contact information). Also, information on labeling issues can be obtained through the Center for Devices and Radiological Health's (CDRH) "Facts-on-Demand," at 1-800-899-0381 (specify #1251 when prompted for the document shelf number).

Availability and Utilization of Emergency Contraception

— *Dr. Felicia Stewart, Henry J. Kaiser Family Foundation*

Currently, there are a limited number of products available for emergency contraception (EC), although the number is growing. The newest product is Preven (Gynetics), which the FDA approved for use in the United States in 1998. Other products include PC 4 (Schering), available in Europe since 1984; Postinor (Gedeon Richter), available in Eastern Europe since 1980, and, more recently Postinor 2 (Gedeon Richter); nine pill products not packaged specifically for EC; and the copper IUD. Preven includes an instruction book, a pregnancy test and emergency contraceptive pills (ECPs). Currently, substantial use of EC occurs only in two western European countries: 2.3 percent of reproductive age women in Finland, and 6 percent in the United Kingdom. Also, millions of women use Postinor in some 36 countries, but the instructions and regimen for Postinor are not the same as for ECPs.

A recent study by Glasier and Baird compared results when routinely providing ECPs and when providing only information before ECPs are needed. With routine provision, use of ECPs increased and more unintended pregnancies were prevented. Of the 549 women given an ECP pack in advance, 47 percent used ECPs at least once in a year and there were 18 unintended pregnancies; among the 522 women receiving only information on ECPs, 27 percent used it and 25 unintended pregnancies occurred. The Washington State Pharmacy

Project, which made ECPs readily available through a broad public education campaign, estimated that from 4 percent to 8 percent of U.S. women would use ECPs if good pharmacy access and public education existed. Currently, there are no good data on ECP use in the United States; some estimate its use at 1 percent.

The 1997 Kaiser Family Foundation Survey found that virtually all obstetricians-gynecologists, nurse practitioners, and family planning providers in the United States knew about ECPs, and a substantial proportion provided ECPs at least once during the year. More than half of these providers discussed EC in an emergency situation, but only about 10 percent routinely discussed EC. The number of providers registered with the national hotline increased from 1,200 in 1997 to 2,700 in 1998. Use is increasing along a continuum. At first, only those who were raped were offered EC. Then providers began to include women who asked and had been exposed on high-risk days, and then to all women who ask. Now, some routine education about EC exists, with easier access by phone or through pharmacies in select locations. Eventually, some locations may routinely provide advance provision.

User knowledge is also increasing. Currently, about 10 percent of women in the United States know ECPs are available and know the time frame for their use. Another 55 percent have heard of ECPs but don't know the time frame for use or that they are available in the United States. The media can increase knowledge of ECPs. The television show, "ER," included a brief scene that involved EC use. A telephone survey by Princeton Survey Research Associates found that knowledge of ECPs increased sharply the week after the show, although the pre-show level returned 10 weeks after the show. Similarly, a 30-second news spot on MTV resulted in 4,200 calls to the national hotline in two days, compared to 133 calls a day on the average. It is hard to tell how much more use of EC there will be, but the curve is clearly going up.

The growing availability of EC also has wider and more fundamental implications. For example, integrating an initial EC dose into routine protocols for beginning other contraceptive options, such as oral contraception, injectable contraception, or vaginal barrier method use, could be explored to allow method start any time in the menstrual cycle. Similarly, couples today no longer select simply a contraceptive method. Rather, they select a strategy. The strategy often involves more than one method, such as condom use backed up by EC, or oral contraceptives with condom use to reduce STD risk in all or some sexual encounters. The era of contraception as a single method has come to an end. ❖

Experience from Recent or Ongoing Barrier Contraceptive Effectiveness Trials

The morning included five presentations on recent or ongoing barrier contraceptive effectiveness trials, summarized below.

Comparing Polyurethane and Latex Condoms

— Terri Walsh, California Family Health Council

The California Family Health Council conducted a comparative contraceptive efficacy study, with 805 couples randomly assigned to use polyurethane or latex male condoms. Couples used the study condom exclusively for six months but were also informed about emergency contraception (EC). Couples used EC only 33 times in the study; they were kept in the study results. To incorporate EC use into reported pregnancy rates, we added an estimated probability of pregnancy that would have occurred had EC not been used. Corrections for even this small number of uses increased the reported typical use pregnancy rates slightly in almost every category of measurement.

The study, conducted from 1994 to 1996 with funding from the National Institutes of Health, measured performance (breakage and slippage), efficacy, usage and acceptability. Less than 5 percent were lost to follow-up, although only 65 percent of the couples completed six months in the study. The major reasons for dropout were personal, such as breaking up with a study partner or moving. Participants were recruited through advertisements in local newspapers, entertainment guides and radio spots. The study population was representative of monogamous couples who use condoms for contraception. The average age was 27, with 15 years of education. About two-thirds were white, 16 percent were Hispanic, 6 percent were African American and 12 percent came from other ethnic groups. About two-thirds were married or living together. The average length of the relationship was 3.4 years. Most participants were experienced condom users. Only 8 percent of men and 3 percent of women were inexperienced (i.e., 10 or fewer uses prior to study). About 3 percent of the women had used EC before entering the study.

When designing the study, we faced an ethical dilemma. Study subjects are able to detect condom failure (breaks or slipoffs) and could use EC to reduce their risk of pregnancy. Should information about EC be withheld? Should subjects be asked to refrain from using EC? The answer to both questions was "No." So the question was: How would access to EC be incorporated into the study? We wanted to provide sufficient information about EC so the women could use it, but we wanted to distinguish between the study requirements and having access to EC. We wanted to create a neutral environment that neither discouraged nor promoted EC use, so that participants could decide what was best for them and would fully report what they did.

Information and access to EC were provided during the study in the following way. We distributed a handout on EC use at the enrollment visit and offered to answer questions. The handout explained when EC might be used, risk of pregnancy relative to time in the cycle, side effects and how to contact us if they decided to use it. When asked about EC, we arranged for participants to receive EC at several clinics and private practices, and we paid for its use. We did not determine the protocols used regarding EC use. We did not suggest or recommend EC use, nor did we try to dissuade participants from using EC. Participants were not discontinued from the study after EC use.

Information was gathered primarily through diaries kept by the couples. When couples requested information about EC use, we recorded as much information as possible. The diaries contained easy-to-use, pictorial icons for condom use, unprotected intercourse, condom breaks, slipoffs and discomfort. About 90 percent of the couples submitted diaries.

Participants had abundant occasions for taking advantage of EC. In the study, there were 37,360 acts of intercourse using the study condoms. But participants did not use a condom in 2,755 unprotected intercourses outside of menses. Also, 418 condoms broke, and 181 slipped off. So, what happened on all of those occasions when pregnancy could occur? To our amazement, not much. Participants used EC only 33 times: two for the 2,755 unprotected intercourses, 21 for the 418 breaks, and 10 for the 181 slipoffs.

In the analysis of pregnancy rates, we adjusted for use of EC. We started by estimating the ovulation date for each cycle of EC use. We calculated the average cycle length based on either study data if available or by history. We assumed that ovulation occurred 14 days prior to the expected menses. Then, we assigned a probability of conception based on the number of days before, on, or after ovulation that the exposure occurred, using estimates reported by Wilcox et al.

Arriving at this estimate of probability was difficult. The variation in each woman's cycle affected our estimates, along with the variability in the luteal phase (although assumed to be 14 days, it can range from 10 to 16 days). In figuring the earliest and latest dates each woman might have ovulated, we arrived at ranges from six to 20 days, and even longer in a few instances. Hence, we felt very uncomfortable about assigning a specific probability of conception for each EC use. For this reason, we calculated the average probability of conception among all 33 EC uses in the study. We then reduced this number by the probability of miscarriage within the first six weeks of pregnancy, where we would not have a clinical pregnancy.

As Table 1 shows (see page 8), we calculated the average probability of conception as 0.1, with a factor of 0.76 to adjust for early miscarriages. Together, this is an adjustment of 0.076 for the probability of pregnancy with EC use. Thus, in the latex group, where there were eight EC uses, the estimated number of pregnancies that would have occurred without EC use was 0.6. The estimated added pregnancies for the polyurethane group was 1.2, for a total estimated added pregnancies to the study of 1.8. Put another way, without the availability of EC use during the study, there would have been an estimated additional 1.8 pregnancies.

Table 1. Correction to Typical Use Pregnancy Rate

	EC Uses	X	Probability of Conception	X	Probability of 6 Week Viability	=	Added Pregnancies
Polyurethane	16		0.1		0.76		1.2
Latex	8		0.1		0.76		0.6
Total	24*		0.1		0.76		1.8

* There were a total of 33 EC uses, but only 24 occurred in the cycles contributing to the pregnancy analysis.

The next challenge was to incorporate this calculation into the typical use and consistent use pregnancy rates for the entire study. Table 2 shows pregnancy rates for the entire study before and after incorporating the risk associated with EC use. To obtain the adjusted rates, we added the 0.076 adjustment for probability of pregnancy with EC use into the appropriate time interval within the life table calculations. With the overlap of the 95 percent confidence interval, none of the differences in pregnancy rates for the two condom groups were statistically significant.

It is interesting to note that the typical use rate for the latex condom adjusted for EC use was the same as the unadjusted rate. This is due to two factors: There were few EC uses in the latex group, and the denominators were different for these two rates. We excluded all data subsequent to EC use when calculating the unadjusted rate, but used all data in the adjusted rate. If the excluded cycles had a lower risk of pregnancy than cycles contributed by women who had never used EC, the unadjusted rates would include a larger proportion of higher risk cycles than the adjusted rates.

In summary, we observed three major findings regarding EC use in a barriers trial. First, participants rarely requested EC appointments when merely provided with an information sheet on EC. Second, participants were more likely to use EC following a condom failure than following unprotected sex. And third, difficulties in determining the day of ovulation of women who used EC make it difficult to determine what the EC correction factor should be.

Table 2. Impact on Pregnancy Rates

	Unadjusted for EC	Adjusted for EC	95% CI
Typical use			
Polyurethane	4.5	5.1	+/-2.6
Latex	7.0	7.0	+/-2.9
Consistent use			
Polyurethane	2.1	2.4	+/-2.2
Latex	1.0	1.1	+/-1.5

Comparing Non-latex and Latex Condoms

— Dr. TMM Farley, UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization (WHO)

Study Background

In early 1996, we conducted a pilot project for a randomized study comparing contraceptive effectiveness of non-latex and latex condoms. The project sought to establish whether acceptability and slippage/breakage studies in selected volunteers could translate to differences in pregnancy rates between the different types of condoms. If this was the case, then equivalence in slippage and breakage rates could be used as a surrogate for equivalence in actual clinical performance in family planning clients. This would reduce the requirement for large scale, difficult and costly contraceptive effectiveness studies whenever a new condom material or innovative condom shape was developed.

The study populations had to represent as closely as possible normal family planning clients who elected to use condoms as their method of contraception. Recruitment was through family planning clinics that provided services to a sufficient pool of condom users annually. Volunteers would remain in the study up to a maximum of 12 months, or until they no longer wished to participate, chose to use another contraceptive method, or chose to use only non-study condoms. Since pregnancy was the primary study endpoint, women were the study unit, though it was expected that the majority of volunteers would be in a stable relationship with a single partner. The pilot study was conducted in three locations with diverse social and economic situations: Chengdu (China), Sagamu (Nigeria) and Manchester (United Kingdom).

What About Emergency Contraception?

Investigators in Manchester raised the question of EC. Their family planning clinic served mainly a university population, and EC was routinely promoted and provided as part of normal clinic services. They felt that recruiting study volunteers who were unaware of EC was impossible, and that it was not ethical to deny EC if a volunteer requested it following a condom break, slip or nonuse. The Manchester site was participating in a WHO study comparing the Yuzpe and levonorgestrel EC regimens, so awareness of EC may have been higher among clients there than in other parts of the United Kingdom. We felt that EC use had to be addressed for any site in the United Kingdom and possibly other countries too. Even if EC had not been promoted in other participating countries in 1996, we anticipated that the situation might change during the study.

U.K. practice at the time of the study was to provide EC through family planning clinics or general practitioners (GPs). While we expected the majority of EC requests would come directly to the study clinic, it was possible that a volunteer might request EC from another source, such as her GP or another family planning clinic, if she were away for a weekend or on vacation. Our study instruments therefore had to record EC requests at the clinic or from other sources. We decided to gather this information through the scheduled follow-up interviews, consulting the daily diary of menses, acts of intercourse and condom use, if available.

Calculating an EC-Adjusted Pregnancy Rate

Because of potential use of EC during the study, we made the rate of EC requests an important additional study endpoint. Reasons for requesting and using EC could completely mask any differences between study groups. For example, a higher rate of no condom use or of condom breaks in one study arm may not translate into differences in pregnancy rates if EC were used. Similarly, even if there were no differences in the rates of no condom use or slips and breaks, differences in the rates of EC requests may indicate that the reliability of the study condoms were perceived differently by the volunteers.

Methods for calculating the pregnancy rates in the absence of EC use are readily available. The number of pregnancies (n) occurring in m months of observation follows a Poisson distribution with $E(n) = V(n)$. Thus, the estimated standard of error of the unadjusted pregnancy rate $r = n/m$ is given by $se(r) = \sqrt{(r/m)}$. Exact confidence intervals for Poisson variables can be computed from the Chi-square distribution (Johnson et al.).

In order to incorporate EC use into the analysis of the primary endpoint (pregnancy), we defined a new statistic, the "EC-adjusted pregnancy rate." For each EC request, we added a fraction of a pregnancy corresponding to the probability of conception on the day of the cycle when the act of intercourse occurred. This provided an estimate of the number of pregnancies that would have occurred if EC had not been used, and gave us a method to adjust for possible differences in the rates of EC use according to study group. The EC-adjusted number of pregnancies $n' = n + \sum_i p_i e_i$, where e_i is the number of EC requests corresponding to acts of intercourse on cycle day i, and p_i is the probability of conception. The EC-adjusted pregnancy rate is $r' = n'/m$.

We also wanted to calculate a standard error and a confidence interval (CI) for the EC-adjusted pregnancy rate. We calculated the standard error and CI treating the r' as if it were a Poisson random variable, but this may not be appropriate. Since the p_i are fixed weights, n' is a weighted sum of Poisson variables and does not follow a Poisson distribution.

To calculate the EC-adjusted pregnancy rate, we also had to determine which conception probabilities to use. A number of authors have provided estimates of conception probabilities according to the day of the cycle, but when we developed the analysis strategy, no consensus on the best rates had been established. We elected to use the smoothed rates of Dixon et al. Revised conception probability estimates computed by formally combining data from all available studies have recently been published by Trussell et al. For a randomized comparative study such as ours, the exact choice of conception probabilities would make little difference. In contrast, the exact choice of probabilities would have more of an impact on studies that provided an unbiased estimate of the true, or absolute, effectiveness rate, or studies that compared condom effectiveness rates in different groups, with EC available to some but not other groups.

Pilot Study Results

The pilot study involved 90 women followed for a maximum of three months. A total of two pregnancies and five EC

requests were recorded in 253.0 woman-months. The five EC requests resulted from reports of two condom splits, one break, one perceived leak, and one intercourse in which no condom was used. The five acts of intercourse occurred on cycle days 4, 8, 13, 16 and 21, or days -10, -6, -1, +2 and +7 relative to the estimated day of ovulation.

Table 3 shows the conception probabilities compared to the estimated day of ovulation. The Dixon conception probabilities are: 17 percent on day -1, 5 percent on day +2, and zero on the other days on which intercourse occurred. This results in an estimated 2.22 EC-adjusted pregnancies (95 percent CI: 0.3 - 7.7) or 10.5 EC-adjusted pregnancies per 100 woman-years (95 percent CI: 1.6 - 36.5). Calculations that used the revised conception probabilities from Trussell et al. yielded 2.3 EC-adjusted pregnancies, corresponding to 10.9 EC-adjusted pregnancies per 100 woman-years.

Anticipated Problems for Main Phase of Study

With the limited number of pregnancies and EC requests observed in the pilot study, little further analysis was possible. However, in the main phase of the study, we plan to recruit 3,000 women and observe 25,000 months of condom use. Currently, EC is only readily available in family planning services in two centers that would each recruit 300 women during the main study. However, EC may be introduced in a third center of similar size. If the rate of EC use in the pilot study is repeated (five requests in 71 woman-months), we would anticipate approximately 500 EC requests. This amount of EC requests would result in a number of problems that will need to be resolved:

1. What is the correct distribution and variance of the EC-adjusted pregnancy rate? Is the naïve approximation using the Poisson distribution adequate?

2. If unprotected intercourse was reported on more than one day leading to the EC request, the probability of conception in that cycle would be computed by combining the specific daily conception probabilities using the model introduced by Schwartz et al. This calculation, while straightforward, would further complicate the distribution and estimated variance of the EC-adjusted pregnancy rate.

3. Many statistical packages are available to analyze event data using the Poisson distribution. They can be used to estimate ratios of pregnancy rates between study groups, as well as to adjust for the impact of potential predictive factors, such as age,

Table 3. Conception Probabilities and EC Requests by Day of Cycle

	Cycle Day (relative to day of ovulation)								
	-5	-4	-3	-2	-1	0	1	2	3
Dixon et al.	6%	10%	15%	17%	17%	14%	9%	5%	2%
Trussell et al.	4%	14%	16%	28%	30%	12%	5%	0%	0%
EC Requests	0	0	0	0	1	0	0	1	0

which may be unbalanced across the study groups. It is unclear how to use such modeling techniques for the EC-adjusted number of pregnancies or the EC-adjusted pregnancy rate.

4. Can life-table methods be used to compute, for example, six- or 12-month cumulative EC-adjusted pregnancy rates? Similarly, can regression models for survival data be applied?

5. EC does not prevent all pregnancies — the recent WHO study reported efficacy rates of 57 percent for the Yuzpe and 85 percent for the levonorgestrel regimens (WHO Task Force). How should we handle cycles where EC is used and a pregnancy is subsequently confirmed? It may be tempting to apply the same algorithm to compute the EC-adjusted number of pregnancies, but attributing more than one pregnancy in a single cycle would be incorrect.

6. Are differences in the efficacy of EC important? In addition to showing differences in efficacy for the levonorgestrel and Yuzpe regimens, the WHO study demonstrated that the efficacy of EC declined with greater delay since intercourse (WHO Task Force). I believe both the type of regimen and time of initiating EC use to be irrelevant to estimating EC-adjusted pregnancy rates. However, I expect there to be considerable debate about the interpretation of the EC-adjusted pregnancy rate if there are substantial differences between study groups in the delay from the act of intercourse to EC use, or differences in the type of EC regimen used. Hopefully, such problems of imbalance will not arise in a randomized study.

Future Plans for Main Phase of Study

The main phase of the study is currently on hold pending funds and availability of suitable condoms. All study instruments have been revised following the pilot study and the main phase could be launched at short notice. We have additionally modified the study to collect detailed slippage and breakage information on all volunteers. Since one of the objectives of the study is to demonstrate whether differences in slippage and breakage rates predict differences in pregnancy rates, it is essential that the slippage and breakage information be obtained in the same study population. We intend to collect details of the first five condoms used at the start of the study and the first five condoms used after the six-month follow-up visit — a double-nested slippage and breakage study. We have not finally decided which condoms to include.

Lea's Shield and FemCap Trials

— *Dr. Christine Mauck, Contraceptive Research and Development Program (CONRAD)*

In the two efficacy studies I will discuss, participants were told to use only the study method and implicitly agreed not to use EC. In the studies, four cases of EC use were reported among more than 1,100 women. Data from these four women were included in the final results because the most appropriate way to handle such data had not been established. This dilemma is in part what prompted this meeting, since FHI was providing considerable assistance to us in data analysis. Of

the coital acts, about 7 percent involved incorrect method use or no contraception, situations where women might want to use EC.

Both of the trials were designed to calculate typical use pregnancy probabilities for the barrier method alone. Both studies were randomized and fairly large. The Lea's Shield study, with 300 women, compared efficacy among women using this device with and without spermicides. The FemCap trial, with about 840 women, compared efficacy of the FemCap device to a diaphragm. Lea's Shield and FemCap are mechanical barrier devices for use by women, similar in some respects to cervical caps and diaphragms, but each with distinctive design features.

Is it ethical to ask women to agree not to use EC? If so, what are the key elements of an informed consent process if women will be asked not to use EC? We, in essence, did ask women not to use EC, although we did not go into any detail about it. In the Lea's Shield trial, the consent form read: "I must be willing to use Lea's Shield as my only form of contraception for six months." The FemCap form read: "I will use [the assigned method] as my only means of contraception." The possible use of EC was not specifically addressed in either trial's consent process. The trials were designed and initiated in the early 1990s, before EC was widely known or available. As awareness and availability increases, I think EC should be specifically addressed.

In the two trials, four women reported using EC — one in the Lea's Shield study and three in the FemCap trial. Some detail on each of these four can provide a flavor of what can actually happen in clinical trials.

The woman in the Lea's Shield trial had sex 28 times in 40 days during the study. All uses were "perfect," meaning the device was used alone and correctly according to the woman's coital log, except for unprotected sex for the 23rd act. This act was on day 14 of the cycle, which would normally be near the day of ovulation except that her previous cycle was 42 days, not 28. She started EC the day after the unprotected sex. Three weeks later, she had a negative pregnancy test. She was kept in the analysis, without any adjustment for a probability of pregnancy from the EC use. This might be handled differently in the future.

In the FemCap study, subject #644 had sex 102 times in 216 days with 83 perfect uses, 16 other method uses (condom), two uses with the device upside down, and unprotected sex on the 15th act with no EC use. One of the times she used a condom (31st act), she also used EC the same day. It is not clear why she used condoms so much or why she used EC this once. The 31st act occurred on day 15 of her cycle, which might have worried her. (Her previous cycle was 30 days.) Twelve days after taking EC, she had a negative pregnancy test. She completed the study and her data were kept in the analysis. Again, this might be handled differently today.

Subject #2105 in the FemCap study had sex four times in eight days. We have no coital logs after the fourth act. All four uses were perfect, but the device was found to have sperm in it on the fourth

act. (She wore it to the clinic, per protocol, and it was checked for sperm after the fit was found to be suboptimal.) She started EC use on the day of this act, which was day 19 of her cycle; her previous cycle was 30 days. Twelve days later, she had a negative pregnancy test. She discontinued the study 54 days later because of inability to fit the device. She probably should have been discontinued at the time of her EC use. She was kept in the treated population, which was used to calculate pregnancy probabilities, but not in the comparison group with the diaphragm. She was excluded from this group not because of the EC use but because of the fitting issue.

Subject # 2116 in the FemCap study had sex 88 times in 190 days. Of these, 81 uses were perfect, five were other method uses (condom), one involved unprotected sex (no EC use), and one involved removing the device early. When the device was removed early, she used EC three days later. This occurred on day 16 of her cycle; her previous cycle had been only 16 days but the cycle before that had been 30 days. She completed the study the day EC was prescribed. She had a negative pregnancy test 30 days later. She was also kept in the analysis.

In the two studies, 7 percent or less of the women either used no method or used the method alone but incorrectly. These are the most likely reasons women would be interested in using EC. If a trial were incorporating information on EC use for a larger portion of women than we had, detailed coital logs might be useful. But in our studies, we determined that overly detailed logs would be difficult to use. Women filled out diary cards, and the study coordinators transcribed that information onto coital logs. We chose not to collect some data, such as the time of insertion and removal and the number of acts during a single insertion. This information would have been helpful but would probably have included many additional data problems, given the number of problems observed on the simpler coital logs.

Efficacy Trial of Spermicidal Agents

— *Dr. Elizabeth Raymond, Family Health International (FHI)*

FHI is currently conducting a randomized trial testing five spermicidal products. The objectives of the trial are to measure and compare contraceptive effectiveness, safety, acceptability and product use. Eleven research centers in the United States are collaborating on the trial, which aims to enroll a total of 1,800 women. Recruitment began in June 1998. The study is scheduled to take three years, which includes 29 months of recruitment and seven months of follow-up for each woman. As of September 25, 1998, 125 participants had been enrolled, and so far, none had requested EC. The study is funded by the National Institutes of Health.

Each participant in the trial will make four scheduled visits to the research center (a screening and admission visit and three follow-up visits) and three phone calls to the center between the follow-up visits. A highly sensitive pregnancy test will be administered at each visit and before each phone call. The

women will keep daily coital and menstrual diaries. The data collected on the diaries include: whether bleeding occurred, whether it was the first day of menses, and for each coital act, the time, method used, and minutes between spermicide insertion and coitus.

The study protocol includes specific policies regarding EC use. Each candidate must agree to use the assigned spermicide as her only method of contraception for 30 weeks, except for emergency contraceptive pills (ECPs). Women are not required to use ECPs at any time. ECPs will be provided free of charge to participants when needed and requested. ECPs will not be provided in advance, that is, upon admission to the study or during follow-up visits before any indication of need. The indications for ECP use are: no method used, incorrect use (e.g., spermicide was not inserted long enough before coitus), method did not function properly (e.g., the spermicide tablet was found not to have dissolved), or other incidents in which the investigator judges that EC use may be needed.

If EC is needed, the investigators will provide either the Yuzpe regimen or a levonorgestrel-only regimen. The Yuzpe regimen is four active Nordette pills to be taken within 72 hours of unprotected intercourse, followed 12 hours later by a second dose. For the levonorgestrel regimen, 20 Ovrette pills are to be taken within 72 hours after unprotected intercourse, followed 12 hours later by a second dose.

At admission, we will collect data on whether the woman thinks she will use EC if an indication arises. We will also collect information on ECP requests and provision, including the date, indication of need, prescription, date and time of coital act prompting need, and dosage provided. After each use of EC, similar data will be collected, including the date, time of use and side effects.

The planned primary study analysis will estimate the "combined method effectiveness" of spermicide backed up by ECPs, if the woman chooses to use them. This analysis will ignore use of ECPs during the study. If a woman who uses ECPs becomes pregnant, she will be counted as having a pregnancy. If she does not, she will be counted as not having a pregnancy.

A secondary analysis will be conducted to estimate the effectiveness of spermicide alone. This analysis will count each ECP use as a fraction of a pregnancy, similar to the method used by the California Family Health Council in their condom study. The fraction of pregnancy will be equal to the probability of clinically detectable pregnancy after unprotected intercourse on the cycle day of the act leading to the ECP use.

Another secondary analysis will be conducted to estimate the effectiveness of spermicides alone. This analysis will exclude women who say at admission that they intend to use ECPs if they have a problem with the spermicide.

True Efficacy Study

— Dr. Markus Steiner, Family Health International (FHI)

Participants in the conference received a copy of a manuscript summarizing this pilot study (Steiner et al.).

A "true efficacy" study design is a new approach to measuring how well a barrier method really works to prevent pregnancy. The true efficacy approach may provide a better measure of how well a barrier method works than the measures obtained from a traditional contraceptive trial. We have successfully tested this approach in a small pilot study.

We are all familiar with the traditional contraceptive trial of barrier methods. A cohort of women is enrolled for a prescribed period of time, usually six months or 12 months. Women are then randomized to use either a standard barrier or a new barrier. The main outcome is the relative difference in the pregnancy probability of the different methods at the end of the study.

The absolute pregnancy probabilities are very difficult to interpret across studies because the design and analysis of studies have changed over the years. For example, today's studies include more sensitive and frequent pregnancy testing and hence are more likely to measure pregnancies that may have gone undetected in past studies. As a result, the absolute pregnancy probabilities may be higher than they would have been in past studies. However, even if all studies were designed and analyzed in exactly the same way, the absolute pregnancy probabilities would still be difficult to interpret because participants differ along factors that influence the risk of pregnancy.

The first factor is the couple's ability to conceive. This factor will vary depending on the couples' age, history of STDs and other health-related variables. Even if a couple is very fecund, if they are having infrequent intercourse or are not having intercourse at the right time of the cycle, they will not get pregnant. So the second factor influencing the pregnancy probability is frequency and timing of intercourse. The third factor is the degree of compliance — how correctly and consistently the method is used.

An example of how participant characteristics can provide a misleading absolute pregnancy probability is a study from the 1970s. In this study, participants used N-9 condoms for two years and reported a 12-month typical-use rate of less than half a percent. A closer look at the men enrolled shows just how misleading the low absolute probability is. Half of the men were over 40 years old, and 20 percent were over age 50. The age of the female partners is not known, but we can assume they were similar in age and were no longer very fecund. Clearly the low pregnancy probability in this study does not demonstrate that N-9 condoms worked. Rather, the couples enrolled most probably had a low ability to conceive and were not having frequent intercourse. In addition, this study only counted pregnancies that ended in a live birth, further lowering the pregnancy probability. Even if the couples had not used any form of contraception, they may have had a similarly low pregnancy probability.

The concept of how many women would have conceived had they not used any method is central to our new "true efficacy" approach. The proportionate reduction in pregnancy is a measure of effectiveness that takes this concept into account. We sometimes refer to this proportionate reduction as "the prevented fraction," which is shown below:

$$1 \text{ minus } \frac{\text{risk of pregnancy in group assigned the method of contraception}}{\text{risk of pregnancy in unprotected group}}$$

This fraction is the true measure of how well a barrier method prevents pregnancy if it is used correctly and consistently.

An example from the EC literature shows how this fraction works. To estimate the effectiveness of EC to prevent expected pregnancies, the denominator in the fraction comes from historical control data. These data show that out of 100 women having one act of unprotected intercourse during the fertile part of the cycle, eight women will conceive. For the numerator, traditional Yuzpe trials have found that out of 100 women using EC within 72 hours of unprotected intercourse, two will conceive. Using the formula, we can then calculate the effectiveness of the Yuzpe regime as .75 or 75 percent:

$$1 \text{ minus } \frac{2/100}{8/100} = .75$$

For this EC calculation, it is important to note that we get the denominator from historical controls. Therefore, in using the formula, researchers have to assume that the ability to conceive is the same for the historical controls as it is for those using EC. This is a significant assumption.

Ideally, we would like to have both the numerator and denominator come from the same population. The true efficacy approach seeks to accomplish this by avoiding the need for any historical controls or comparisons with previous studies. This approach uses other strategies to control for the factors that influence the risk of pregnancy: ability to conceive, frequency and timing of intercourse, and compliance.

To estimate the participant's ability to conceive, we recruit women who want to conceive but are willing to postpone pregnancy by one cycle. This enables us ethically to randomize women to use no method of contraception. From the group randomized to use no method, we can estimate the whole cohort's risk of pregnancy had they used no method. In other words, we now have a valid estimate of the denominator in our equation.

To control for frequency and timing of intercourse, we ask participants to have intercourse on certain days of the cycle. In our pilot study, we gave women home ovulation kits. They were asked to abstain from vaginal intercourse from the beginning of the study until their day of ovulation, when they should have intercourse. They were also asked to abstain for five more days after ovulation. Since we enrolled participants during their menses, they had to abstain for about ten days, have intercourse once, and then abstain for five more days.

Controlling for compliance may be the most difficult factor. Our pilot study enrolled women for only one cycle, so we think this short duration minimized non-compliance. Another strategy to minimize non-compliance was to have participants call an automated toll-free number once a

day to answer a few questions about their coital activity, method use and menstrual bleeding. Of course, we cannot be absolutely certain that all participants were perfectly compliant with the protocol, but due to randomization, we think the level of compliance in the different arms was similar.

The primary question with this approach was whether we could successfully complete such a study. In our pilot study, we enrolled 58 women at three sites. One site enrolled 25 women in five months. This level of recruitment is similar to the speed of recruitment during traditional barrier trials. We assigned women to use either the male condom, a spermicidal film or no method, when they had intercourse on their day of ovulation. We had a relatively low loss to follow-up with 54 women completing the study. We feel that this pilot study demonstrated the feasibility of this approach on a small scale.

This small study does not have the precision to tell us the effectiveness of the two methods. Even so, it is useful to show how effectiveness would be calculated in a larger study of this design. The study found that the group using no method had a 12 percent pregnancy probability, while the spermicidal film group had an 11 percent pregnancy probability. None of the 19 women assigned to use condoms conceived.

Using the formula shown above, we estimate that the effectiveness of the film is 8 percent while the effectiveness of the condom is 100 percent. Put another way, the film reduced the pregnancy probability from 12 percent to 11 percent, while the condom reduced it from 12 percent to 0 percent. We do not know how much this prevented fraction could be generalized to other cohort groups with different participant characteristics. However, we think the prevented fraction could certainly be generalized with more confidence than can the absolute pregnancy probabilities from a traditional trial.

We have just received USAID funding for the full-scale study that we plan to initiate in the coming year. In this study we will use the same two approved products that we used in the pilot study: male condoms and spermicidal film (VCF). We hope to have a total of 500 women complete this study — 200 women per group assigned to the two methods and 100 women in the no method group. Given our assumptions, this should provide sufficient power to detect a statistically significant difference between condoms and VCF.

We estimated the size for the full study based on several assumptions. We decided to ask participants to have two acts of intercourse. The first act will be 17 days prior to the next expected menses while the second one will be on the day of ovulation. Based on the most recent review of probabilities for different days of the cycle (Trussell et al.), we estimate that 13.6 percent of the participants in the no method group will conceive during the study. We assume that 0.2 percent of the condom group and 4.0 percent of the VCF group will conceive. The condom probability comes from the most recent edition of *Contraceptive Technology*, while the VCF probability comes from FHI's recently completed international spermicide trial (Raymond et al.).

The prevented fractions for condoms and VCF are assumed to be 98 percent and 70 percent respectively. The prevented fraction for condoms is close to what we measured in the pilot study (100 percent compared to 98 percent), while for VCF, the two prevented fractions are very different (8 percent and 70 percent). The outcome of most interest in the full study is to see how different the prevented fractions really are. With 500 participants completing the study, we will have 85 percent power to find a difference, given our assumptions.

So what do we see as the future of this approach? Clearly the next step is to demonstrate that a full-scale study is possible to conduct. ❖

Summary of Issues Raised Because of EC Availability

— Rosalie Dominik, Family Health International (FHI)

Participants in the conference received a copy of a background paper by Rosalie Dominik, James Trussell and Laneta Dorflinger that addresses in detail the issues summarized in this presentation (Dominik et al.).

As a result of the growing availability and acceptance of emergency contraception (EC), new issues need to be considered when designing a barrier contraceptive effectiveness trial. The assumption behind these new issues is a general objective to determine how well a barrier method works.

Before the EC era, the primary objective of new barrier method effectiveness studies was to measure the typical use pregnancy probability for a new barrier method when used alone. Another possible objective was to compare this measure to the typical use pregnancy probability of an existing barrier method. For example, trials of the cervical cap versus the diaphragm, the sponge versus the diaphragm, and the Reality female condom all assessed what I would like to call the *method specific effectiveness*. The pregnancy probability estimates from these studies are best interpreted as the probability of becoming pregnant for women who plan to use the barrier method alone to prevent pregnancy. In the EC era, we may still be interested in determining the method specific effectiveness.

We now might also be interested in measuring the *combined method effectiveness* of a barrier method with EC backup. This can be estimated by the typical use pregnancy probability for women who plan to use the barrier method with EC backup if needed, for example, after a malfunctioning of a device or after an episode of nonuse. This typical use pregnancy probability would be interpreted as the cumulative probability of becoming pregnant among women who plan to use the barrier method with EC backup if indicated.

Ideally, we would estimate precisely both the method specific effectiveness and combined method effectiveness for a variety of potential users of a new barrier method. We cannot assume that the availability of EC will reduce the risk of pregnancy by the same amount for different barrier methods. Two barrier methods that are equally effective when used alone may have different levels of effectiveness when used with EC as a backup. This may be the case because problems may be more easily recognized for one method than another, and consistency of using the two methods may vary as well. For example, a new barrier method that has a better method specific effectiveness than the standard latex male condom might have a worse combined method effectiveness than the standard latex male condom.

The first question raised by the availability of EC is whether measures of both the method specific and the combined method effectiveness are needed to evaluate sufficiently a new barrier method. And if both are needed, is one more important than the other? Some may think that the answer to these questions should vary by method. For example, it may become standard practice to provide all acceptors of barrier methods that must be obtained

by prescription with a prescription for EC as well. If this is the case, then combined method effectiveness may be of greater interest for a prescription-only barrier method. However, for a method that women will be able to obtain over the counter, there may be more reason to measure method specific effectiveness. Regardless of which measurement is the primary objective for a study, design and implementation issues arise that we did not have to deal with before the EC era.

Several issues arise when the primary objective is to assess the method specific effectiveness of a new barrier method. The first issue is whether it is ethical to ask women enrolling in a barrier method study to agree *not* to use EC. Historically, women enrolling in barrier method trials have agreed not to use other methods of contraception besides the assigned barrier method, even though use of an additional method — for example, use of a male condom in a diaphragm trial — would provide extra protection against pregnancy.

I'm not aware that the ethics of asking women to rely solely on their assigned method was ever questioned prior to the EC era. This new ethical concern may be due to the fact that EC gives a woman a chance to reduce her risk of pregnancy after a method malfunctions or after nonuse.

Assuming it is considered ethical to conduct a trial where women are asked not to use EC, then we must decide what information about EC should be provided during the informed consent process. We need to make sure that women understand what they are giving up by agreeing to rely on the barrier method alone without EC backup.

Once women have given fully informed consent not to use EC and have enrolled in a method specific effectiveness trial, issues related to EC still arise. Even if a woman has agreed not to use EC during the trial, she may ask for EC during the trial, for example, because the condom she was assigned to use broke. What should she be told? What if a woman reports that the condom broke yesterday, but she does not request EC? Should clinic staff be specifically instructed not to bring up EC in this case in a method specific effectiveness study? Should the counseling be the same if the woman reports an episode of nonuse but doesn't request EC? Certainly all investigators in a multicenter study should be asked to approach these situations in the same manner.

Even if EC is not supposed to be used in a study, some women will likely use it anyway. What data on EC use should be collected in a method specific effectiveness trial? And if EC use is reported, how should it be handled in the primary analysis? One option is to analyze just the data as is, that is, not do anything special because EC was used. The resulting typical use pregnancy probabilities would be interpreted as the cumulative risk of pregnancy among women who intend not to use EC.

Another option is to count women who use EC as having a fraction of a pregnancy, assuming no protection was provided by

the barrier method on that day. The value of the fraction is set equal to the expected probability of pregnancy given the cycle day of intercourse that led to the EC use. This calculation involves making a number of assumptions, but it provides some estimate of what the pregnancy probability would have been had EC not been used. Simply excluding cycles of EC use from the analysis or stratifying the data by whether or not EC was actually used is not appropriate, as the background paper explains in more detail.

So, even if one decides to do a study in which women are asked not to use EC, one still has a lot of new issues to think about when developing a study protocol. Now I will turn to issues that arise when planning a study of combined method effectiveness.

A goal to measure combined method effectiveness implies that women would be asked at enrollment to agree to use EC whenever certain events occurred. If they do not use EC when indicated, their behavior would be considered incorrect method use. A question then arises: Should the trial exclude women who indicate that they would not use EC? One would need to exclude such women if the study objective is truly to assess the risk of pregnancy among women who consider the barrier method plus EC backup when indicated to be their primary method of contraception.

However, if the study enrolls women who do not expect to use EC even if it is indicated, the instructions for use should clearly describe EC as an *option* rather than as a standard backup. The typical use pregnancy probabilities estimated from a study where EC backup is considered optional might be thought of as a weighted average of the typical use pregnancy probabilities that would be obtained from a method specific effectiveness trial and from a combined method effectiveness trial.

Another question to consider is how to provide EC to the participants. At least three options are possible. First, the protocol might require that all women be provided an EC packet at admission and a replacement packet when their supply is used. Second, all women could be offered EC at admission — they need not accept it — and could be provided a packet any time they request one. Third, EC might be distributed only when a need arises. That is, women might be given the backup method only if they report nonuse or a malfunctioning of the barrier method.

If the study goal were to estimate the risk of pregnancy under optimal conditions for adherence, the first option would be the best approach — unless possessing an EC packet changes one's consistency of barrier method use.

However, if the goal is to estimate the probability of pregnancy in normal-use settings, whether the method is available over the counter or only by prescription may determine whether providing EC in advance is the best. For a barrier method that will probably not be available over the counter, advance provision of EC during a trial may result in a study with too optimistic an estimate of pregnancy probability. That is, when outside the trial setting, women using this barrier method will need to make a special trip to a health-care provider to obtain EC backup.

A related question concerns the instructions that women should receive regarding when to use EC. Should they be instructed to use EC after every problem with a device or only after specific kinds of problems? Should they be instructed to use EC after every unprotected act or only if these events occur mid-cycle? Should women be asked to consult the investigator in all cases to help determine whether EC should be used? Instructions related to these questions need to be standardized across centers.

In a combined method effectiveness trial, the primary analysis is straightforward because EC is considered part of the method being evaluated. But there may be some interest in trying to assess the method specific effectiveness as a secondary objective of a combined method effectiveness study. There are at least two possible approaches.

One approach is to count each use of EC as a fraction of a pregnancy as discussed earlier. This approach will provide a measure of what the typical use pregnancy probability would have been had EC not been used.

A second approach could be applied if the trial includes women who at admission indicated that they would not use EC. Then we can estimate the typical use pregnancy probability separately for this subgroup. A typical use pregnancy probability estimate for this subgroup would be interpreted in the same way we would interpret a typical use pregnancy probability obtained from a method specific effectiveness trial.

It is important to note that these two approaches might lead to different typical use pregnancy probability estimates, for several reasons. The fractions of pregnancies needed for the first approach might come from an external population of women whose average fecundity is different from the study population. Also, women who do or do not plan to use EC may differ in coital activity, consistency of product use and average fecundity.

Finally, when the effectiveness of a barrier method is evaluated in a combined method effectiveness trial, how should the product label report effectiveness?

The last question on the agenda for this afternoon asks the group to reflect on what role the true efficacy trial that Markus Steiner described might have in the evaluation of new barrier contraceptives. Might studies such as the true efficacy study provide sufficient data to characterize a new barrier method? ❖

Afternoon Discussion

– Dr. Willard Cates, Jr., Moderator, Family Health International (FHI)

The afternoon discussion was a freewheeling dialogue. Designed to focus on a series of questions raised in the final morning presentation, the discussion evolved in a fluid way, with participants speaking from their own experience and interests. The originally posed questions merged in different ways, depending on the viewpoint and scientific issue that participants raised. The discussion, in the end, fell into five general categories, presented below. The sequence generally follows the practical decisions researchers have to make:

- what question to address
- how to provide emergency contraception (EC)
- how to calculate study results
- how study designs and analyses affect labeling
- whether a new study design is a viable option for consideration.

What Do We Want To Know about the Effectiveness of Barrier Contraceptives?

The group reached a near consensus that the most important function of a clinical trial of a barrier method is to assess the effectiveness of the barrier method alone. The effectiveness of the combined method of a barrier method with EC as a backup was a secondary goal. Since the primary purpose is to provide information to consumers on the effectiveness of barrier methods alone, researchers need to measure what some refer to as the method specific effectiveness (MSE).

Knowing the effectiveness of barrier methods alone is important. Women who use barrier methods may not want to use hormonal methods, including emergency contraceptive pills, so they need to know the MSE for barrier methods. Users of barrier methods may not know about EC or have access to it. Thus, MSE for barrier methods is the primary piece of information these users need.

However, the group also agreed that researchers cannot ethically prohibit a woman from using EC. Participants felt that researchers have to provide EC during a trial if a woman wants it. This ethical mandate exists even if a woman agrees at the beginning of the trial to use only the method being tested and not EC. Thus, measuring MSE will be difficult.

If barrier method effectiveness alone should be measured but EC should be provided during the trial, what information would a trial need to gather? The trial would need accurate data on use of the barrier method, on EC requests and use, on menses, and on consistent and correct use during all cycles, not just those when pregnancies occurred. Also, it should document and report what women were told about EC during the informed consent process and how they were counseled about EC. Some participants also expressed interest in seeing if the decision to request EC as a backup varied by when in the cycle unprotected intercourse occurred.

Even if detailed and accurate data on all coital acts and EC uses are collected, it may not be possible to extract meaningful estimates of the MSE from trials where EC is available (see "How Should Researchers Calculate Study Results," page 26). Despite this warning, the majority of participants wanted to evaluate the MSE of barrier methods in trials where EC is provided as backup. The analysts were charged with the task of doing the best they could to extract meaningful MSE measures from trials where EC is used.

A long discussion took place regarding how to characterize the type of trial the group seemed to want. Would it be best to think of such a trial as an MSE trial? Would it be preferable to consider it as a combined method effectiveness (CME) trial, with a primary analysis that adjusts somehow for EC use? Would it be better to consider this type of trial to be a multiple option method (MOM) trial, with the options being either the barrier method alone or the barrier method plus EC? Finally, one participant commented: "We're getting caught up in semantics." The group concluded it wanted to get method specific effectiveness while allowing for use of EC.

Should EC be Provided in Advance or upon Request?

The group was about evenly divided on whether to provide EC in advance or upon request. Participants made strong arguments for both points of view and raised questions about research issues that need addressing.

One argument for advance provision concerned the issue of controlling the study environment. By providing EC in advance during a research trial, the study can standardize access to EC. If EC is not provided ahead of time, women may use EC in haphazard ways, depending on their perception of need and availability in the community where they live. By standardizing EC provision, study results may be easier to interpret.

Some participants argued that advance provision would make research results relevant to the real-world environment (at least in the United States) that women may encounter when the results are available in the future. Several proponents of advance provision felt that the availability of EC was increasing rapidly. Consequently, EC should be provided ahead of time in the trial to simulate what the practical world may be like when the study results are available. "We're trying to establish what the standard of care should be," said one proponent. (It is worth noting that this argument also reflects the group's desire to obtain meaningful measures of CME even though MSE was judged to be of primary interest.)

Skeptics of advance provision in a trial pointed out that women overseas will not have access to EC in the near future. Thus, the trial should not provide it in advance because this is not standard practice among providers. By providing it in advance, researchers would be adding an unnecessarily artificial element to the trial. Also, providing EC in advance might tend to increase its use, thus making the results for the MSE more difficult to calculate.

Participants expressed interest in studying how provision of EC would affect the use of barrier methods with EC as a backup. In fact, research on advance provision might be more of a service-delivery issue than a research question for a clinical trial. How to provide EC in a research trial in order to arrive at the most accurate measure of MSE in an ethical way may be a different issue than how we want to provide it in clinical practice.

A recent study by Glasier and Baird in Edinburgh, Scotland, examined advance provision as a service delivery issue. They compared a treatment group of 549 women who were supplied EC pills to keep at home with a control group of 522 women who could use EC by visiting a doctor in case of an emergency. After a year, almost half of the treatment group (47 percent) used EC at least once, compared to about one fourth (27 percent) of the control group. There were 18 unintended pregnancies in the treatment group compared to 25 in the control group. The women in the treatment group were not more likely to use EC repeatedly, and the two groups used other methods in a comparable fashion. "Making emergency contraception more easily obtainable does no harm and may reduce the rate of unwanted pregnancies," the study concluded. Research on the issue of advance provision of EC is currently under way in Ghana by FHI and in India and Zambia by the Population Council.

The topic of protocols about advance provision emerged, but the issues involved were not discussed in-depth. For example, one of the questions not addressed directly was the condition under which women should be told to use EC as backup. For example, should the provider tie this advice to when in the cycle the misuse, nonuse, or problem with the method occurred? If a trial provides EC in advance, researchers should not communicate that there is a "safe period" for unprotected intercourse when EC use is not necessary.

How Should Researchers Calculate Study Results?

Two general ways exist to calculate pregnancy probabilities in barrier method trials where EC is sometimes used. First, calculations can estimate the effectiveness of using a barrier method with EC as a backup if women choose to use it. This calculation approach leaves women who use EC in the primary analysis and does not have to make statistical adjustments. Put simply, it ignores the use of EC. If a woman who uses EC becomes pregnant, she will be counted as having a pregnancy. Otherwise, she will be counted as not having a pregnancy. Labeling of the barrier method would have to be adjusted, because use of EC would presumably lower the pregnancy rates in the trial. The consumer would have to be informed of that fact. Moreover, if EC is used frequently, this calculation approach provides more of a CME measure than an MSE measure.

The second general approach is to attempt to calculate a pregnancy probability for using a barrier method alone — that is, to extract a measure that better reflects MSE. This requires a statistical adjustment for each time EC is used. Statistically, one counts all EC uses as a fraction of a possible pregnancy; the fraction would be equal to the probability of a clinically

detectable pregnancy occurring after unprotected intercourse on the cycle day of the act leading to EC use.

A major concern of some participants is the potential for large-scale use of EC, which would cloud results so that they are not meaningful as a measure of MSE. In the only large-scale trial to date that has used a statistical adjustment approach, summarized by Terri Walsh of the California Family Health Council in the morning session, only 33 women used EC. Adjustment for EC use did not substantially alter estimated pregnancy probabilities. In that trial, EC was not provided in advance. Participants were informed about EC use at enrollment, but study staff neither encouraged nor discouraged EC use. If EC is provided in advance and discussed with participants more frequently, some think that much higher use may occur during a trial. This could result, as one participant put it, in "the tail wagging the dog." That is, the amount of EC use could be a greater determinant of the reported pregnancy probability than the issue at stake: the effectiveness of the barrier method itself.

One way to address the larger-scale use of EC is to stratify the women at the beginning of the trial according to their intent to use EC. The FHI spermicide trial being conducted in 11 U.S. research centers will use this approach in one secondary analysis. To estimate the effectiveness of spermicides alone, a secondary analysis will exclude women from the analysis who say at admission that they intend to use EC if they have a problem with the spermicide.

Neither the adjustment nor the stratifying approach will solve the statistical problem perfectly. The background paper by Dominik et al. provides a more detailed discussion of these issues.

How Do the Studies Affect Product Labeling?

Several important points emerged during this discussion. Researchers pointed out that the best we may be able to offer from trials is an effectiveness range rather than an exact percentage. Because of EC use, the best calculation may be a range. Participants brainstormed about what labels might say, depending upon the audience. A women's advocate pointed out that men would not be interested in labeling on condoms about EC use because women use EC. A participant from the FDA suggested that it might be useful to do research to see what women and men want to see on a label.

Several participants from the FDA also made the point that they were open-minded about how to approach labels for new barrier methods. They welcomed advice from the research community on how to design and analyze barrier method trials and seemed to welcome suggestions for a standard protocol for barrier method trials. It is important to devise something that is reasonable, even if it is not what the FDA is currently using.

Research designs need to consider what the future is likely to be, because the study results may affect labeling in the future. Study designs could even affect how a manufacturer chooses to market a condom or spermicide product — whether, for example, the marketing is linked with EC.

Is the True Efficacy Study a Viable Option for Consideration?

The participants discussed the potential role in trials of the true efficacy design described in a morning presentation. A true efficacy trial is a randomized trial comparing a barrier method to no method (or to another barrier method); it includes women who desire pregnancy but are willing to delay pregnancy for a short period. The group was generally optimistic about the future of this research approach.

Several participants questioned whether the ease of using a method would affect results. As currently proposed, the trial records use of a barrier method during just one cycle. Is just one use enough for measuring true efficacy, or would more practice in using the method correctly be needed? For example, a spermicidal product might be more difficult to use correctly than a condom. One suggestion was to lengthen the study to two cycles rather than one. Another was to allow a practice period with the barrier device. Others pointed out that this approach would not allow for testing other issues, such as safety, which require longer-term use. Participants thought it would be useful to try this approach with the products being used in the spermicide trial that FHI is now coordinating. ❖

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AGENDA

Evaluating the Effectiveness of Barrier Contraceptive Methods: Impact of Emergency Contraception

September 23, 1998 ◆ Hyatt Regency Hotel ◆ Bethesda, Maryland

8:00–8:30	**Registration and Continental Breakfast**
8:30–8:45	**Introduction to Workshop** *Rosalie Dominik, Family Health International*
8:45–9:30	**Effectiveness of Available Barrier Methods** *James Trussell, Princeton University*
	Update on FDA Efforts to Standardize Labeling for Contraceptives *Colin Pollard, CDRH, U.S. Food and Drug Administration*
	Availability and Utilization of Emergency Contraception *Felicia Stewart, Henry J. Kaiser Family Foundation*
9:30–9:45	**Break**
9:45–11:30	**Experience from Recent or Ongoing Barrier Contraceptive Effectiveness Trials**
	NIH Polyurethane versus Latex Condom Trial *Terri Walsh, California Family Health Council*
	WHO Non-latex versus Latex Condom Trial *Rosalie Dominik, Family Health International* *for Tim Farley, World Health Organization*
	CONRAD Female Barrier Trials (FemCap versus Diaphragm; Lea's Shield) *Christine Mauck, Contraceptive Research and Development Program*
	NIH Effectiveness Trial of Spermicidal Agents *Elizabeth Raymond, Family Health International*
	True Effficacy Study *Markus Steiner, Family Health International*
11:30–12:00	**Summary of Issues Raised because of Emergency Contraceptive Availability** *Rosalie Dominik, Family Health International*
12:00–1:00	**Lunch**
1:00–3:15	**Discussion** *Moderator: Willard Cates, Jr., Family Health International*
3:15–3:45	**Wrap-up** *Rosalie Dominik, Family Health International*

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