ectopic pregnancies, or had signs or symptoms suggesting that they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. A total of 2,121 women were enrolled in the two studies including 859 women who were in the ≤ 49 days group, which is the gestational age which is the subject of this application.

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography and women were assigned to the appropriate gestational age group.

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took three 200 mg tablets of mifepristone orally in the presence of the investigator. Patients did not eat for one hour before and after the consumption of the mifepristone. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. Patients did not smoke during the 48 hours following mifepristone consumption and on the day misoprostol was administered. Patients then remained at the clinics under observation for at least four hours. Adverse events such as nausea, vomiting, diarrhea, abdominal pain, and vaginal bleeding were rated by the women and recorded. Blood pressure and heart rate were measured at least hourly. Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 as "spotting", "normal", or "heavy." During this period, the women were also monitored for the expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a vacuum aspiration or dilatation and curettage constituted a failure. A surgical procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. The efficacy analysis, therefore, included 2015 women. No additional information is available on the outcomes of the 5 women with continuing pregnancies who were lost to followup. All other women with continuing pregnancies were aborted surgically.

Efficacy was 92% in the ≤ 49 days group with a lower 95% confidence interval of 90%. This is somewhat less than the 95.5% efficacy with a lower 95% C.I. of 94.2% reported in the pivotal French studies upon which approval of this application was recommended.

Efficacy was 83% in the 50-56 days group with a lower 95% confidence interval of 80%. Efficacy was 77% in the 57-63 days group with a lower 95% confidence interval of 74%.

The 92% success rate in the ≤ 49 days group is an acceptable one.

The median duration of bleeding in the ≤ 49 days group was 14 days. The average duration of bleeding was 16 days. This is considerably longer than the average duration of 9 days reported in the French studies upon which approval of this application was recommended, but is an acceptable duration.

Excessive bleeding necessitated blood transfusion in only 1 patient in the ≤ 49 days group and required hospitalization of only 2 patients in the ≤ 49 days group. An additional 2 patients in the ≤ 49 days group were treated in the emergency room for excessive bleeding. Thirteen (2%) patients in the ≤ 49 days group required surgical intervention because of excessive bleeding. Bleeding was managed by the administration of uterotonic agents such as oxytocin, methylergonovine or vasopressin in 5% of patients in the≤ 49 days group.

The adverse event rates were higher in these studies than those in the pivotal French studies upon which approval of this application was recommended. This is shown in Table 5.

Table 5

Frequent Adverse Events (≤ 49 days) in French and U.S. Trials

Adverse Event	French Trials	U.S. Trials
Abdominal pain (cramping)	83%	96%
Nausea	43%	61%
Headache	2%	31%
Vomiting	18%	26%
Diarrhea	12%	20%
Dizziness	1%	12%

The majority of adverse events were of mild or moderate severity. The difference in the frequency of common adverse events noted above is acceptable.

In the pivotal French trials, 5.5% of subjects had a decrease in hemoglobin of greater than 2g/dL while in the U.S. trials, 7.8 % of patients in the ≤ 49 days group had such a decrease. This difference is an acceptable one.

The U.S. clinical trials confirmed the findings of the pivotal French trials that mifepristone and misoprostol are safe and effective in terminating pregnancies of up to 49 days gestation even though the success rate in the U.S. trials was lower

than that of the French trials. This lower success rate might be related to the lack of experience of most of the U.S. investigators with medical abortion. The lower success rate might also be attributable somewhat to the fact that in the U.S. trials, a woman's request for a surgical termination any time after receiving mifepristone was honored and classified as a failure rather than being excluded form the efficacy analysis. However, in the ≤ 49 days group, less than 8% of the failures (5 patients) were because of patient requests.

The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age. The majority of surgical interventions were for incomplete abortion and excessive bleeding.

This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.

Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility including at least a four hours stay after the administration of the misoprostol.

In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).

In the U.S. clinical trials, an increase in the incidence of some adverse events (vomiting, nausea, diarrhea, uterine hemorrhage) occurred in the 50-56 and 57-63 days gestational age groups compared to the ≤ 49 days group. The safety profile of the ≤ 49 days group in the U.S. study did not differ significantly from the pivotal French studies, even though the incidence of common adverse events in the U.S. clinical trials was higher than that of the French trials in the ≤ 49 days group. The percentage of patients in the U.S. studies and the French studies requiring hospitalization, requiring blood transfusion and experiencing heavy bleeding was about the same. However, about 1.6% of the patients in the ≤ 49 days group in the U.S. study had surgical intervention because of heavy bleeding compared to less than 1% of patients in the French studies. The average duration of bleeding was 16 days in the U.S. studies compared to 9 days in the French studies.

While the U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical

abortions with gestations of 49 days duration or less, they demonstrate that with longer durations of gestation (50-56 days and 57-63 days), the treatment regimen is less effective and the incidence of adverse events is higher.

A comparison of medical termination of pregnancy with surgical termination is of interest in a polulation of women who are given a choice to select between medical and surgical termination of early pregnancy. Such a comparative clinical trial was conducted according to a uniform protocol from 1991 to 1993 in urban clinics in China, Cuba, and India, three countries where abortion is legal and available. A total of 1373 women with amenorrhea ≤ 56 days were given a choice of surgical abortion or mifepristone and misoprostol in the same dosage regimen as used in the U.S. studies. The results of this study were published in 1997. The medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India). In each site failure rates of medical abortion increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients. The only serious complication was excessive bleeding in medical abortion patients, which is a reason for surgical intervention and for dissatisfaction among medical abortion patients. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients. Slightly higher proportions of medical than surgical patients were dissatisfied (8.8% versus 3.8%). Despite the bleeding pattern and the failure rate of the medical abortion method, particularly in China, medical abortion by the mifepristone and misoprostol regimen was said by the authors of this published study to be safe, efficacious, and highly desired by and acceptable to women in developing countries.

The results of a smaller study published in 1999 comparing mifepristone to surgical abortion in U.S. women are consistent with the findings of the larger comparative clinical trial done in China, Cuba, and India. The study was a nonconcurrent, prospective, cohort analysis of 178 mifepristone - misoprostol and 199 suction curettage abortion subjects with intrauterine pregnancies ≤ 63 days gestational age. The medical abortion cohort represents all of the subjects enrolled at one U.S. clinical site for the mifepristone clinical trial between December, 1994 and August, 1995. The surgical abortion cohort was enrolled prospectively at the same clinical site between November, 1995 and December, 1996. Overall, 18.3% of medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (R.R. 3.93; 95% CI 1.87,8.29). The risk of failure demonstrated a statistically significant upward trend from 3.3 to 4.4 with advancing gestational age. Four mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine

mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4). Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients. The use of antiemetic agents during the abortion procedure was significantly more common in mifepristone patients than surgical patients (31.1% versus 1%). Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients (RR 7.4, 95% CI 4.7, 11.5). Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients (0.6%) (RR 117.9, 95% CI 16.7, 834.7).

Although the mifepristone and surgical abortion techniques are both safe and effective, the abortion and post-abortion experiences differ significantly as reported in the two published studies above that permit direct comparison of the two techniques in a prospective manner.

IX. Labeling Evaluation:

Comments regarding labeling revisions were transmitted to the sponsor in a letter dated September 18, 1996. Revised draft labeling was submitted by the sponsor June 25, 1999 and currently is under review.

X. Conclusion:

The results of the U.S. studies do not adversely differ significantly from the results of the two pivotal French clinical trials which were the basis for the approvable letter to the sponsor September 18, 1996.

XI. Recommended Phase 4 Studies:

The medical officer, in his revised original NDA review, recommended that phase 4 studies with the following objectives be conducted:

A. To monitor the adequacy of the distribution and credentialing

system.

B. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

C. To assess the long-term effects of multiple use of the regimen.

D. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

E. To study the safety and efficacy of the regimen in women (1) under
18 years of age, (2) over age 35, and (3) who smoke.

F. To ascertain the effect of the regimen on children born after treatment failure.

The phase 4 recommendations were included in the approvable letter to the sponsor dated September 18, 1999.

XII. Consideration of Advisory Committee Members' Comments:

Part of the review process for this application included seeking expert advice from members of the FDA Reproductive Health Drugs Advisory Committee at a public meeting July 19, 1996. The committee voted 6-0 (with two abstentions) that the pivotal studies (French studies) presented at that time showed that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The studies presented to the committee involved women treated within 49 days of the beginning of their last menstrual period.

Preliminary safety data from recently completed U.S. trials were also presented.

The committee recommended some phase 4 studies and individual committee members offered some individual comments for consideration by the FDA staff, particularly comments regarding labeling and the drug distribution system. All comments were carefully and fully considered and, to the extent possible, implemented.

The applicant was asked September 18, 1996 to submit a comprehensive description of the proposed distribution system. The following complete response from the applicant was submitted to FDA August 18, 1999 regarding the distribution system:

"The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.

- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.

- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.

- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:

  - The ability to accurately confirm the duration of pregnancy

  - The ability to determine blood Rh factor

  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgment from the patient that they have been provided with the product label, that they have read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.

- Place the dose # on the acknowlegement and in the patient record.

- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.

- Fill out and return AE (Adverse Event) cards to the distributor, identifying patient by dose # only.

- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.

- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to insure that the drug is only supplied to qualified physician/hospitals who register with the distributor, that the patient is given access to the product label and that the product # is placed on the acknowledgment in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use."

FDA requested six phase 4 studies of the applicant's August 22, 1996 (and reminded them of their commitment to perform them in the approvable letter dated September 18, 1996). The requested studies are listed below:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

The applicant's complete response was submitted to FDA August 18, 1999 regarding the requested phase 4 studies as follows:
"We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows all women who have surgical abortions following failed mifepristone abortion, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

   We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifeprostone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. We are willing to supply treatment failure data from a sample of providers for a mutually agreeable period to time, for instance six months or one

year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under age 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those who smoke will be collected in the sample of women we have agreed to study, as described in item Number 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated."

Other issues raised by individual advisory committee members are addressed below:

While the DOSAGE AND ADMINISTRATION section of the labeling states that mifepristone may be administered by or under the supervision of a physician trained in abortion, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities, the applicant has not mentioned anything about conducting training seminars for use of mifepristone, without financial incentive to physicians, and distributing the drug only to those physicians who completed the training. Perhaps the applicant will address this point when the details of the distribution system are submitted to FDA.

The applicant should be able to assess compliance with return visits of patients in the phase 4 studies to be performed.

A surgical termination, if needed, should be provided at no additional cost to the patient. It should be part of the mifepristone-misoprostol method of abortion.

Reasonable attempts to contact patients who do not return to confirm the abortion should be made by the physician.

The applicant intends to monitor the distribution system to ensure that only qualified physicians are treating patients.

The applicant will monitor the number of failed medical terminations and any resulting surgical complication.

The applicant will examine central registries of mifepristone users in Europe to determine what can be learned about multiple use. In addition, the applicant proposes to attempt to develop a cohort of women in future studies in the United States who report more than one use of the regimen and agree to be followed.

The applicant has some data on women who were more than 35 years of age, on women who smoked, and on women under 18 years of age. They will submit an analysis of safety and efficacy data on these subgroups. In addition, data on these subgroups will be collected during the phase 4 studies.

The outcomes of pregnancies not terminated by medical or surgical abortion should be followed up and reported by the physician. This should be part of the credentialing and distribution system.

Conditions of exclusions in the clinical trials are in the labeling.

There is no age restriction in the labeling. Women under 18 years of age or over 35 years of age were arbitrarily excluded from the clinical trials, but there is no biologic reason to think that the efficacy and safety of drug administration to these age groups is any different from that of women 18-35 years of age.

The labeling states that misoprostol should be taken two days after ingesting mifepristone.

Women who smoked at least 10 cigarettes per day were excluded from the French studies. Women in the French studies were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day misoprostol was to be administered.

Women in the U.S. studies were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Women were excluded from the U.S.

studies if they were over 35 years of age, smoked more than 10 cigarettes per day, and had another risk factor for cardiovascular disease. The labeling contains a cautionary statement that women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. The labeling does not contain a statement that alcohol and/or tobacco should be avoided during treatment. Myocardial infarction has been associated with the administration of an intramuscularly administered prostaglandin, sulprostone, but no such association has been reported with the administration of misoprostol. The labeling for misoprostol does not contain any statement regarding avoiding smoking.

Several comments regarding labeling were made by individual advisory committee members and have been throughly considered.

Overall, I do not think that the labeling imparts an impression to the physician or patient that the treatment regimen is "free of adverse effects and free of actually serious side effects."

The use of mifepristone and misoprostol extends the options available to women for the elective termination of early pregnancy, but it is inappropriate to directly compare this regimen with surgical termination in terms of adverse events. For example, bleeding and cramping are to be expected with mifepristone and misoprostol and not generally expected with surgical termination. The two methods are usually appropriate for abortion at different gestational ages. Medical abortions are done usually during the fifth to seventh weeks of gestation. Surgical terminations are usually not done before the sixth week of gestation.

Reference to drugs known to cause enzyme induction has been deleted.

The risk of malformation occurring if pregnancy is not terminated after drug administration appears in table 2 of the labeling.

The labeling states that a surgical termination must be recommended for patients who have an ongoing pregnancy because of the risk of fetal malformation resulting from the treatment procedure.

The physician labeling mentions that although specific drug interactions have not been studied, it is possible that interactions could occur with drugs like aspirin or other non-steroidal anti-inflammatory agents that modify or inhibit prostaglandin synthesis and metabolism. The only available study, however, found no evidence that non-steroidal antinflamatory drugs inhibit the ability of misoprostol to induce uterine

contractions and expulsions. In the patient labeling, the patient is instructed to advise her medical provider of all the medications she is taking and not to take any of them or any other medications during the treatment procedure without first telling her medical provider.

The mifepristone labeling states that since the effects of mifepristone on infants are unknown, and it is not known if misoprostol or its active metabolite is excreted in human milk, breast feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days following administration of the medications.

The labeling for misoprostol states that it is not known if the active metabolite (misoprostol acid) is excreted in human milk, and therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Two days is the optimal time to administer misoprostol after the administration of mifepristone because mifepristone requires 36-48 hours to sensitize the uterine muscle to prostaglandins. This information could be added to the labeling.

We do not know if, or to what extent, effectiveness decreases if administration of misoprostol is delayed past two days after the administration of mifepristone. We do know that administration of misoprostol 36-48 hours after the administration of mifepristone is well founded, based on the mechanism of action. The labeling does state that misoprostol should be administered two days after administration of the mifepristone.

Most of the data available are from women 18 years of age or older. However, the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those over the age of 18 years.

Consideration should be given to including a statement under PRECAUTIONS in the physician labeling that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies of greater than 49 days.

Consideration should also be given to including a statement in the patient labeling under "Are there any reasons that I should not have the treatment procedure?" that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies greater than 49 days. This could follow the statements in the patient labeling that state,

"You should not have the treatment procedure if your medical provider determines that the duration of your pregnancy is more than 49 days. For many women this means that the first day of your last period was more than 49 days ago."

The physician labeling contains a PATIENT INFORMATION section that includes the statement, "Before giving you any medication, your medical provider will ask you to sign a statement that you have decided to terminate your pregnancy, and that you have read and understood this information." An ACKNOWLEGEMENT is included in the PATIENT INFORMATION section for the patient and medical provider to sign. Consideration should be given to adding the statement, "My medical provider has confirmed that I am pregnant and that the pregnancy is not greater than 49 days" and a statement that, " My medical provider has discussed with me alternatives to medical abortion including surgical abortion and continuation of this pregnancy."

Everyone who was a member of the advisory committee when mifepristone was presented and who is still a special government employee was sent the results of the U.S. studies in the form of a copy of the article, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States" by members of the Population Council published in the April 30, 1998 issue of the New England Journal of Medicine. The article accurately and succinctly summarizes the results of the studies.

XIII. Recommendation:

Approval of this application is recommended provided that the labeling is satisfactorily revised and the complete details of the distribution system which are yet to be submitted are acceptable.

Medical Officer, HFD-580

1/27/00

April 2, 1996

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

It was a pleasure to visit your site on March 18-20, 1996 to audit the Mifepristone/Misoprostol study. I was grateful for [redacted] me and cooperation during the audit which allowed me to finish ahead of schedule.

During the audit a complete review of the regulatory files was performed and found to be complete. A review of 17 case report form books found the data to correspond to the source documents with the exception of unreported adverse events (not serious in nature) for patient #001 and other minor corrections for 7 additional patients.

Thank you for the efforts put forth by you and your staff throughout the course of the study.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 1 of 86

MIF 000615

FAX

Date March 8, 1996

Number of pages including cover sheet 2

To: Dr. Poppema
Aurora Medical Services
1207 N. 200th, Suite 214
Seattlw, WA 98133

From:

Phone

Fax Phone

CC:

Phone

Fax Phone

REMARKS:

☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Thanks for faxing directions to your site. If my flight comes in at 1:55 PM as scheduled I should arrive between 3 and 4 PM on Monday, March 18th.

Prior to my arrival would you be so kind as to verify that the following documents are on file in the regulatory binder.

- IRB update due 3/95
- letter to the IRB re: Study closure
- signed protocl-pages (with original signature, not copies) for the 10/13/94 and 5/5/95 protocols.

Also, a list is attached of case books that will require RDSI corrections to be made and/or filed in the corresponding case report form books. It would be helpful if these were pulled in preparation for my visit.

Thanks for your help. I look forward to meeting you on the 18th.

The following case books will require RDSI corrections:

#115, #121, #142, #145, #147, #149, #150, #151, #163. + 154

The following case books have corrections to be filed:

#001, #020, #048, #067, #070, #072, #073, #078, #081, #084, #094, #108, #112, #113, #114, #118, #119, #131, #135, #137, #138, #140, #164, #130, #136, #141, #145, #147, #151, #158, #159, #160

February 23, 1996

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

This is to confirm an appointment to conduct a Clinical Quality Assurance audit at your site on March 18-21, 1996.

Please have available for review case report forms, medical records, and the regulatory binder. A random audit of 17 cases will be performed. Several additional RDSI queries will be addressed and copies of completed queries will be filed in charts as well.

Thank you for your cooperation. I look forward to meeting you and your staff on the afternoon of March 18th. Please feel free to call should you have any questions.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 4 of 86

February 21, 1996

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

As we approach the final stages of the Mifepristone/Misoprostol study, we are conducting GCP audits of all sites which will be followed by closures of all sites. During these processes we will be discussing with you and your staff the need to maintain proper records and as importantly, the need to be able to access all patient records (source documents) which support the data recorded in the CRFs. This becomes an issue when patients are referred from satellite centers to the study site. We must maintain records at the study site which support the study.

If a satellite center or central (records) requests "their patients" records we need to determine how to do this logistically to maintain the integrity of the source documents. If your center might be subject to such a request, please contact me so we can document how this will be handled.

If you have any questions, please feel free to contact me.

Thank you for the hard work to date.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 5 of 86

C 3

PHONE CONTACT

Initiator: [redacted] **Date:** December 4, 1995

Contact: [redacted] **Time:** 2:00 PM

Tel No.: [redacted] **Site:** Dr. Poppema/ 166A Ctr. 3

Purpose: M&M Study
Drug Log Update

Summary of Conversation:

[redacted] telephoned me on 12/4/95 to inform me of a change on the drug dispensing log. She mentioned that the dates under the mifepristone column on line #3 and line #4 for patients #003 and #004 should read 11/9/94.

Pending Issues:

None

Action Steps:

A copy of the updated log will be retrieved at the close out visits.

cc: [redacted]

PHONE CONTACT

Initiator: [redacted] **Date:** November 28, 1995

Contact: [redacted] **Time:** 12:00 PM

Tel No:: [redacted] **Site:** Dr. Poppema/ 166A Ctr. 3

Purpose: M&M Study
Patient #159 [redacted]

Summary of Conversation:

I telephoned Dr. Poppema on 11/28/95 regarding patient #159 [redacted] I asked Dr. Poppema to correct the patient initials to [redacted] on page 10. Dr. Poppema updated the patient initials on the pink CRF page.

Pending Issues:

None

Action Steps:

Copies of the updated CRF pages were faxed and forwarded to

cc: [redacted]

THE POPULATION COUNCIL -28-95 PROTOCOL 166A/B

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
3	02	101	___	8/4/95 (M/D/Y)

PELVIC EXAMINATION

	(circle)		(circle)
Fibroids	No Yes	Pelvic Inflammatory Disease	No Yes
Adnexal Masses	No Yes	Cervicitis	No Yes
Adnexal Tenderness	No Yes	Vulvo-Vaginitis	No Yes

Status of Cervix: ☐ open ☑ closed

Comments: Vagina: small amount bright red blood
cervix: small amount atrophy

Abortion Status: ☑ complete abortion ☐ incomplete abortion ☐ ongoing pregnancy

Confirmed by: ☑ pelvic examination ☑ transvaginal ultrasound
☐ products of conception removed from vagina/cervix

If patient clearly has an incomplete abortion or ongoing pregnancy, conduct surgical abortion and complete page 11.
If abortion was complete or probably complete, conduct exit interview.
If uterine bleeding is continuing, conduct exit interview and schedule follow-up.

BLEEDING STATUS

Was medical intervention required to stop uterine bleeding? (circle o) No Y

If yes: ☐ D&C ☐ hormonal therapy ☐ manual vacuum aspiration ☐ electric vacuum aspiration

Date of cessation of uterine bleeding: ___/___/___ (M D Y)
(check against patient diary) unknown → 11-15-95

PHONE CONTACT

Initiator: [redacted] **Date:** November 21, 1995

Contact: [redacted] **Time:** 12:00 PM

Tel No.: [redacted] **Site:** Dr. Poppema's site

Purpose: Determine [redacted] position in the mifepristone/misoprostol research study

---

Summary of Conversation:

I telephoned the site in Seattle, WA and asked [redacted] what was the responsibility of [redacted] throughout the mifepristone/misoprostol research study. I was informed that [redacted] was the nurse practitioner on the study. She started approximately in January or February. Prior to her employment, [redacted] as the nurse practitioner. They both performed patient examinations.

Pending Issues:

Need a memo to study file pertaining to [redacted] status in this study.

Action Steps:

A memo was placed in both [redacted] and the Population Council's files.

cc: [redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 9 of 86

MEMORANDUM

TO: File

FROM: [redacted]

DATE: November 21, 1995

RE: Mifepristone/Misoprostol Study

[redacted] is the nurse practitioner for the mifepristone/misoprostol research study at Dr. Poppema's site.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 [redacted]
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November 20, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

Once again it was a pleasure visiting Aurora Medical Services, Inc. on November 15, 1995. I appreciate the time your staff allotted me to address corrections on previously monitored case report forms.

During this visit ——— and I addressed queries on patient #'s 124, 130, 134, 136, 141, 143, 144, 145, 146, 147, 150, 151, 152, 157, 158, 159, 160, 161, 162 and 163. Corrections were performed by placing the original white and yellow CRF pages on top of the respective pink page needing the correction. ——— signed/dated all corrections.

In addition, one database query was addressed on patient #49 ——— which was generated by ——— data management. The original form was completed and signed/dated by ———. A copy of the completed query remains in the patient's CRF notebook and the original was returned to ———

Please be advised that there will be a close-out visit in the near future. At this time, the clinical study regulatory binder will be completely reviewed.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 ———
Exhibit 7 Page 11 of 86

November 9, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol 166A)

Dear Dr. Poppema:

This letter will serve to confirm my visit to Aurora Medical Services, Inc. on November 15, 1995. I will arrive at your facility at approximately 8:30 AM and depart when the work is complete. Upon my arrival please have available the medical records/source documents and case report forms (CRFs) for patient #'s 124, 134, 136, 141, 143, 144, 145, 146, 147, 150, 151, 152, 157, 158, 159, 160, 161, 162, and 163.

During this visit [redacted] nd I will be addressing queries on the above listed patients which have been generated by [redacted] quality assurance team. We may need to refer to the corresponding CRFs and source documents for these patients. Please have the CRFs and medical records accessible during this visit.

Thank you for your time and cooperation. If you have any questions, please do not hesitate to call me at [redacted]

I look forward to working with you again soon.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 —
Exhibit 7 Page 12 of 86

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

October 25, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 North 200th Street
Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

As we discussed last week, I plan to visit your clinical site on December 4, 1995. The purpose of this visit is to provide the Population Council an opportunity to directly review the regulatory files and patient data which you are maintaining for the Mifepristone study. These visit are done with the complete knowledge and agreement of the _____ group and are generally categorized as quality assurance visits.

During my visit I would like to review several patient records randomly selected from the first 20 patients you have enrolled in Mifepristone study. This would included source documentation as well as case record form information. Also I would like to look through your regulatory documentation book to determined if you have the latest Protocol on file and the appropriate IRB reviews of Protocols, informed consents, and adverse events.

I plan to arrive at Aurora Medical Services at 9:00AM on the morning of December 4, 1995, and hope to spend 3 to 5 hours during the clinic visit. You do not have to be present during this entire time, but I would certainly hope to have to opportunity to meet you and review any points of information you may wish to present to me.

October 5, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure visiting your facility on September 25-29, 1995. I appreciate the time you and your staff allotted me to review the completed case report forms (CRFs) and medical records.

During this monitoring visit, (35) CRFs for patient #'s 124, 130 and 132-164 were verified against the source documents for accuracy and completeness. Most CRFs and source documents were found to be in excellent shape, despite some minor corrections and clarifications to the CRFs during this visit. Please note that CRF pages 10 and 12 for patient #157 —— as well as pages 10, 11.1 and 11.2 for patient #159/—— , remain at your facility for completion. The pages will be reviewed and retrieved during the next visit. Also, database queries were performed. A photocopy of the completed query sheet remains at the site while the original was returned to ———— addition, several database queries which were completed at —— were filed in each patient's CRF. Furthermore, corrections were performed on patient #'s 81, 84, 87, 104, 113, 117, 118, 120, 128 and 129 by placing the white and yellow CRF pages on top of the respective pink page needing the correction. ———— performed and signed/dated the corrections.

My review of the source documents discovered that certified letters should be forwarded to all patients which are considered lost to follow-up. ———— mailed registered letters to patient #'s 036, 048, 072, 076, 080, 082, 084, 089, 104, 113, 118, 129, 133 and 140 during this visit.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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? no: 159

Please be advised that patient #'s 150, 154 and 158 should be contacted via telephone in order to obtain the "date of cessation of uterine bleeding". To explain, according to the source documents these patient's had minimal bleeding or spotting on Visit 3. — ——— ecorded their "date of cessation of uterine bleeding" as the date of Visit 3. I was informed that the nurse practitioner assumed that if a patient had minimal bleeding or spotting on Visit 3, she did not need to follow-up with these patient's in order to obtain the patient's actual stop bleeding date. According to the protocol in Section 6.3 Visit 3 (Exit Interview, Day 15 of Study), it states "subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated."

The Regulatory Clinical binder and Study Drug Inventory Log were reviewed. The following items were observed:

(1) The laboratory medical test site license #MTS-0705 expired on 10/31/94. During my visit the site administrator, ——— located a valid and updated license #MTS-0705 expiring on 10/31/96. During the next visit, a photocopy of the updated license will be retrieved for ——— files.

(2) ———. mentioned that she had not received an Investigator's Brochure for this study. Enclosed please find a copy of the Investigator's brochure dated September 30, 1994 which should be placed in the binder.

(3) The regulatory binder contained one (1) of three (3) required protocol signature sheets. Two signature sheets were absent from the binder. Enclosed please find two protocols and protocol signature sheets dated May 5, 1995 and October 13, 1994. Please review and sign/date on the lines indicted for the investigator signatures and dates. All protocols and signature sheets should be inserted in the notebook with the July 15, 1994 protocol and signature sheet.

(4) A total of four (4) medication device inventory sheets were forwarded to this facility. The dates on the sheets are 5/3/95, 3/21/95, 1/19/95 and 11/8/94. The 11/8/94 was absent from the notebook. Enclosed please find this document and insert it in the regulatory binder along with the other 3 Medication/Device Inventory Sheets.

Please be advised that there is no remaining study drug at your facility. I performed a complete drug accountability on all the remaining study medication. All study drug was 100% accounted for and your documentation reflected the calculation. I signed and dated the drug inventory log and recorded the drug accountability, as well as returning all remaining study drug to ———

It was a pleasure meeting you and working with ——————and your staff. I look forward to working as a them again soon.

If you have any questions or concerns, please do not hesitate to call me at ——————

Thank you for your time and cooperation.

Sincerely,

[redacted]

Thank you again for your cooperation and I look forward to meeting with you and your staff.

Sincerely,

/S/

Aurora Medical Services Inc, PS

1207 North
200th Street
Suite 214

Seattle
Washington
13

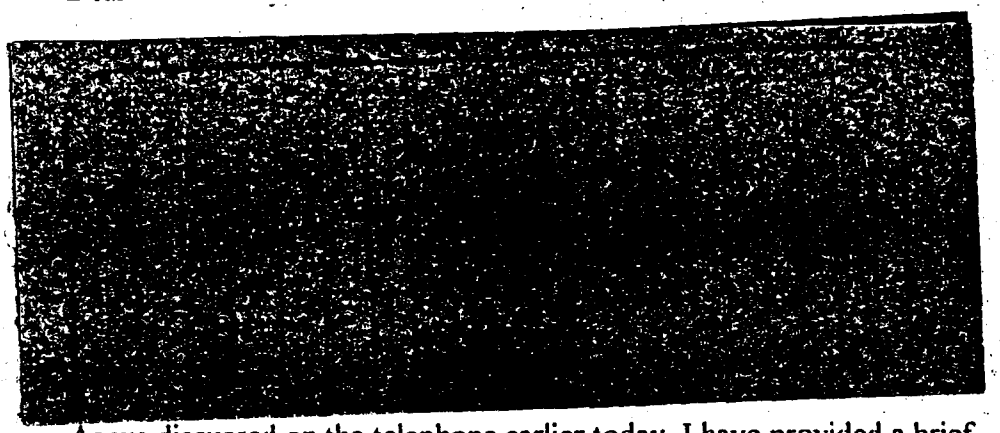
(206) 546-8891
FAX 546-9641

September 6, 1995

[redacted]

RE: Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amennorrehea of up to 63 days.

Dear [redacted]



As we discussed on the telephone earlier today, I have provided a brief description of the circumstances surrounding each of the participants who were lost to follow-up. (see attached page).

The check should be made payable to:
Aurora Medical Services
1207 N. 200th Street
Suite 214
Seattle, WA 98133

APPEARS THIS WAY
ON ORIGINAL

Thank you again for your attention,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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#32 —— Visit 1,12/20/94, Visit 2,12/22/94. Expulsion observed post misoprostol. Pt. moved to California, did not RTC for visit 3. No forwarding address. Message left with friend. No response as of 9/95.

#76 —— Visit 1, 2/22/95, Visit 2, 2/24/95. No expulsion observed.Pt. went to ER 2/27/95 with bleeding. Rx'd Doxy, Methergine, and Tylenol. No show for visit #. No response to repeated phone calls. Letter sent 4/6/95. No response as of 9/95.

#84 —— Visit 1, 3/1/95, Visit 2, 3/3/95. No expulsion observed, but no sac seen by vag. U/S. No showed for visit 3 - three times. Letter sent 6/16/95. No response as of 9/95.

#89 —— Visit 1, 3/1/95, Visit 3/3/95. No expulsion observed. No show for visit 3. Telephone disconnected. Letter sent 4/6/95. No response as of 9/95.

#95 —— Visit 1, 3/8/5, Visit 2, 3/10/95. No expulsion observed. No show for visit 3. Telephone disconnected. Pt. moved. Letter sent 4/18/95. No resonse as of 9/95.

#100 —— Visit 1, 3/15/95, Visit 2, 3/17/95. No expulsion observed. No showed for visit 3. telephone disconnected. Letter sent 4/26/95 and again via certified mail on 5/30/95. Returned unclaimed.

#104 —— Visit 1, 3/29/95, Visit 2, 3/31/95. No expulsion observed, but sac no longer visable by vag. U/S. No showed ofi visit 3. No response to phone calls. Letter sent 6/16/95. No response as of 9/95.

#118 —— Visit 1, 4/12/95., Visit 2, 4/14/95. Possible expulsion before misoprostol. No sac seen with U/S/. No showed for visit 3 - three times. Letter sent 6/30/95. No response as of 9/95.

#129 —— Visit 1, 5/3/95, Visit 2, 5/5/95. Possible expulsion prior to misoprostol. No show for visit 3. No response to repeated phone calls. Leter sent 6/16/95. No response as of 9/95.

#133 —— Visit 1, 5/17/95, visit 2,5/19/95. No expulsion observed but no sac seen by vag. U/S. No show for visit 3. No response to repeated phone calls. Letter sent 6/23/95. No response as of 9/95.

#162 —— Visit 1, 8/2/95, Visit 2, 8/4/95. No expulsion observed. No show for visit 3. No response to phone calls as of 9/6/95.

August 31, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol 166A)

Dear Dr. Poppema:

This letter will serve to confirm my visit to Aurora Medical Services, Inc. on September 25-28, 1995. I will arrive at your facility at approximately 3:00 PM on September 25, 1995 and depart on September 28, 1995 at 5:00 PM. Upon my arrival please have available the medical records/source documents and case report forms (CRFs) for patient #'s 124, 130 and 132-139.

During this visit I will be verifying the CRFs against the source documents for accuracy and completeness on the above listed patients. Also, we will complete queries for patient #'s 49, 56, 63, 69, 70, 74, 76, 77, 81, 84, 87, 95, 98, 105, 106, 113, 117, 118, 120, 128, 129 and 131 which have been generated by ——— data management. We may need to refer to the corresponding CRFs and source documents for these patients. Please have the CRFs and medical records accessible during this visit.

In addition, a complete drug accountability will be performed as well as a review of the regulatory binder.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 20 of 86

Thank you for your time and cooperation. If you have any questions, please do not hesitate to call me at [redacted]

I look forward to working with you soon.

Sincerely,

/S/

[redacted]

PHONE CONTACT

Initiator: [redacted] **Date:** August 31, 1995

Contact: [redacted] **Time:** 4:30 PM

Tel No.: [redacted] **Site:** Dr. Poppema/ 166A Ctr. 3

Purpose: M&M Study
To discuss CRF instructions for protocol 166A

Summary of Conversation:

During a previous telephone conversation, [redacted] questioned if she should complete the header information on the CRF pages which were not utilized. I informed [redacted] to complete the header information and draw a line through the rest of the CRF page. She also mentioned that she would like to review all 164 CRFs and source documents for accuracy and completeness. I suggested that a review of all 164 CRFs was not necessary unless she had a specific reason. [redacted] explained that she had discovered discrepancies when comparing the CRFs to the source documents. For example, she mentioned that the concomitant medication "Tylenol" was administered for cramping. The adverse event of cramping was recorded on page 12 of the CRF and in the "action taken" column drug therapy was documented. Tylenol was the drug of choice for cramping and was recorded on the concomitant page 13 of the CRF. The stop date documented in the medical records for Tylenol extended past the stop date recorded for cramping on the concomitant medication page 12 of the case report form. [redacted] asked if the stop date of Tylenol should be extended to reflect the source documentation. I replied that we would need to review the source documents and the CRF to determine the stop date of the Tylenol.

[redacted] wanted to review the outcome column on the AE page as previously discussed (refer to phone contact 8/29/95). We agreed that a review of the outcome column is acceptable. I again stressed not to change or write on the pink copies of the CRF pages until further notice.

Pending Issues:

Pending fax list of patients. I received the fax on 9/12/95.

Action Steps:

Review fax and discuss with [redacted] during the monitoring visit on 9/25-28/95.

cc: [redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 22 of 86

PHONE CONTACT

Initiator: [redacted] **Date:** August 29, 1995

Contact: [redacted] **Time:** 1:00 PM

Tel No.: [redacted] **Site:** Dr. Poppema/ 166A Ctr. 3

Purpose: M&M Study- Schedule a Monitoring Visit

Summary of Conversation:

[redacted] (study coordinator) and I agreed on a date for a monitoring visit for September 25-29, 1995. During our discussion, [redacted] had the following concerns:

1) She noticed that the study drug relation on the adverse event page 12 of the CRF should be changed on a few patients. She mentioned that the investigator incorrectly completed this field. I suggested that [redacted] fax me a list of patient numbers so that [redacted] can determine if a correction is necessary. [redacted] was also informed not to write on the pink copy in the case report form until further notice.

2) She was concerned about monitoring inconsistencies from [redacted] CRAs in completing the Adverse Event outcome columns. For example, a patient was lost to follow-up for Visit 3, while an adverse event was reported with an unknown stop date during the study. One CRA preferred to record unknown for the outcome while another utilized #3 = unchanged. I suggested that [redacted] continue to follow protocol to complete the CRFs. All concerns will be further discussed/clarified during my visit.

I will contact [redacted] prior to my arrival to confirm arrangements.

Pending Issues:

Pending fax with patient numbers.

Action Steps:

Monitor site on September 25-29, 1995.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 [redacted]
Exhibit 7 Page 23 of 86

August 17, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

I would like to take this opportunity to introduce myself to you and your staff. My name is _____ and I am assuming the monitoring responsibility for the Mifepristone/Misoprostol study at your site.

I will be in contact with you or your study coordinator shortly to introduce myself and arrange a monitoring visit.

I look forward to meeting you and your staff. If you have any questions, please call me at _____

Sincerely.

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 24 of 86

PHONE CONTACT

Initiator: [redacted] **Date:** August 16, 1995

Contact: [redacted] **Time:** 4:00 PM

Tel No.: [redacted] **Site:** Dr. Poppema/ 166A Ctr. 3

Purpose: M&M Study/Introduction - Monitoring Visit

Summary of Conversation:

I telephoned the study coordinator [redacted]) to introduce myself and schedule a monitoring visit. [redacted] mentioned that [redacted] is on vacation until September 7, 1995. However, she would be able to answer questions during a monitoring visit. I asked [redacted] about her availability. [redacted] works Tuesday through Fridays and would be available on the following days: 8/22 - 25/95, 8/30-31/95, 9/5/-8/95. I explained to [redacted] that I am in the process of scheduling several visits and I would call her back shortly to confirm a date.

Pending Issues:

Confirmation of visit date.

Action Steps:

I called [redacted] and confirmed a monitoring visit for 9/11-13/95. [redacted] mentioned that she would be in the office on Monday 9/11/95.

[redacted]

August 9, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

As you have seen from recent communications, we are approaching the end of the Mifepristone/Misoprostol study. In order to start to wind down the study, the Population Council has asked us to stop patient enrollment in a staggered fashion across the country. Therefore we are requesting that your center enroll no more subjects beyond August 10, 1995. If this is impossible, or if you have any questions please feel free to call me as soon as possible.

We will be monitoring your center for all outstanding subjects as before, and will do an additional study closure visit. We want to thank you and your staff for all the hard work to date and look forward to working with you as we bring the trial to a close.

Again if you have any questions please feel free to let me know.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 26 of 86

July 24, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
107 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

We are approaching the end of the mifepristone/misoprostol study. We anticipate that the study will be completed during the month of August. In anticipation of this, we will begin notifying centers as to when to recruit and enroll the last subjects at their center.

Based upon patient enrollment to date, we are stopping recruitment/enrollment in Group 2. Do not recruit and enroll any more patients with amenorrhea of 50-56 days. Thus we are only enrolling patients in Group 3 (57-63 days of amenorrhea).

We want to thank you for all the hard work to date. If you have any questions, please feel free to call. We will be in touch.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 27 of 86

July 28, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

As always, it was a pleasure visiting your clinic on July 12-13, 1995. I appreciate the time your staff allotted me to review the completed case report forms and medical records.

During this monitoring visit thirteen (13) completed case report books were reviewed, corrected and retrieved. Except for some minor corrections and clarifications of some adverse events data, all of the case report forms and source documents were found to be in excellent shape.

Data discrepancies from previously collected case report books were also corrected during the monitoring visit,. All discrepancies were resolved and the case report forms were returned to

Regulatory Clinical Trials Binder and the Study Drug Inventory Log were reviewed and found to be in good shape. It should be noted that the study medication/dispensing log is being kept on an individual bottle basis.

If you have any questions or concerns please do not hesitate to call me.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 28 of 86

June 12, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

As always, it was a pleasure visiting your clinic on May 23-25, 1995. I appreciate the time your staff allotted me to review the completed case report forms and medical records.

During this monitoring visit twenty-four (24) completed case report books were reviewed, corrected and retrieved. Except for some minor corrections and clarifications of some adverse events data, all of the case report forms and source documents were found to be in excellent shape.

Data discrepancies from previously collected case report books were also corrected during the monitoring visit,. All discrepancies were resolved and the case report forms were returned to ———

Regulatory Clinical Trials Binder and the Study Drug Inventory Log were reviewed and found to be in good shape. It should be noted that the study medication/dispensing log is being kept on an individual bottle basis.

Each bottle of 51 tablets of mifepristone has been assigned an individual log sheet, instead of logging in the entire shipment at once. This method, although unusual, is acceptable as long as the total inventory is accounted for and empty bottles are returned to

If you have any questions or concerns please do not hesitate to call me.

Sincerely.

/S/

June 7, 1995

Executive Director
Aurora Medical Services, Inc.
1207 North 200th Street, Suite 214
Seattle, WA 98133

Dear

In response to your June 1, 1995 letter we would like for your center to continue to enroll patients beyond 150. Your center will be reimbursed at the rates specified in your budget for medical and surgical as were the first 150.

We look forward to continue working with you and your center, and thank you for your hard work to date.

I'll be in touch.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 31 of 86

June 2, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in inducing Abortion in pregnant Women with Amenorrhea of up to 63 Days.

Dear Dr. Poppema:

Enclosed please find a summary sheet for the Adverse Events to date in the above referenced study. In addition, we have enclosed a copy of all the Med Watch forms in chronologic order with an AE number written in the top right corner.

Please let this replace your AE section in your binder. This will be updated on a monthly basis.

If you have any questions, please feel free to contact me.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 32 of 86

May 8, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

Attached is a copy of a Non-Participant Patient Questionnaire to be completed by all patients who are not excluded by study criteria but decline to participate prior to signing an informed consent.

Please ensure that this form is completed when applicable if your site is not already doing so.

Thank you for your cooperation. Please feel free to call with any questions.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 33 of 86

THE POPULATION COUNCIL PROTOCOL 166

CENTER NUMBER	SCREENING NUMBER	DATE
____ ____	____ ____ ____	____/____/____ M D Y

NON-PARTICIPANT PATIENT QUESTIONNAIRE

Complete for all patients who are offered the possibility of trying the medical abortion method and are not excluded by study criteria but decline to participate at any point prior to signing an informed consent.

We are trying to find out something about the reasons that women would prefer not to use a medical abortion method. Would you mind answering 5 quick questions? Neither your name nor any way of identifying you will appear with this information.

Age: _____.

Ethnicity/Race:

- ☐ African American
- ☐ East Asian
- ☐ Hispanic/Latina
- ☐ White
- ☐ Other: _____

Social Circumstances:

- ☐ Married, living with partner
- ☐ Unmarried, living with partner
- ☐ living without partner

Have you had an induced abortion before today?

- ☐ Yes
- ☐ No

Why did you choose not to try a medical abortion method? (Do not prompt patient, check all that apply)

- ☐ Did not want to be in a study.
- ☐ Afraid of new drug/experiment.
- ☐ Method requires too many visits.
- ☐ Afraid of a lot of/long bleeding.
- ☐ Afraid of pain.
- ☐ Afraid to see embryo.
- ☐ Method fails too often.
- ☐ Want quicker result/procedure.
- ☐ Other (specify): _____

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 34 of 86

May 4, 1995

Dr. Suzanne T. Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Based upon the meeting held at The Population Council's Offices on May 2, 1995, it was determined that enrollment in Group 1 (patients with amenhorrea of ≤ 49 days) is complete. Therefore, no additional patients should be enrolled into this Group. Enrollment will continue into Group 2 (amenhorrea of 50 to 56 days) and Group 3 (amenhorrea of 57 to ≤ 63 days). The informed consent is being modified to reflect the data which were presented at the meeting. As soon as the modified informed consent has been finalized, it will be forwarded to the centers for IRB approval. For centers utilizing the IRB under the auspices of ———— this will be done for you and the approved amended documents will be sent to you.

If you have any questions, please feel free to call.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 35 of 86

May 2, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure working with _____ during my monitoring visit on April 26-27, 1995. I appreciate the time your staff allotted me to review the case report forms and medical records.

During this monitoring visit five (5) previously monitored case report forms were corrected, completed and retrieved. Also, during this visit twenty-one (21) newly completed case report books were monitored. All twenty-one (21) case report books were corrected and retrieved. Except for some minor corrections and the clarifications of some adverse event data, all of the case report forms and source documents were found to be in excellent shape.

Data discrepancies from previously collected case report books were also corrected during this monitoring visit. All discrepancies were resolved and the case report forms were returned to _____

During this visit, it became apparent that an additional five (5) patients were "Lost to follow-up" after receiving both mifepristone and misoprostol. This raises the total number of patients "Lost to follow-up" to six (6) at this study center. This particular group of patients has become alarmingly high based on the national average. It is clearly documented in these patients' charts that every effort has been made to re-schedule these patients. These efforts included multiple telephone calls over long periods of time and mailed letters. Perhaps, discussing in detail the importance of a Day 15 evaluation and/or the dangers of not having a Day 15 follow-up visit at both the

screening visit and following the ultrasound on Day 3 could possibly lower the number of patients lost to follow-up after misoprostol. Once again every effort should be made to assure that patients return for the Day 15 evaluation while the patients are still present in the clinic.

If you have any questions or concerns please do not hesitate to call me.

Sincerely.

/S/

[ ]

April 27, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

Enclosed please find additional study medication (153 tablets) for the Mifepristone/Misoprostol Study.

Please sign and date the medication inventory form, photocopy for your files, and return to my attention in the enclosed self-addressed stamped envelope.

Thank you for your continued cooperation.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 38 of 86

MEDICATION/DEVICE INVENTORY

SPONSOR: Population Council

PROJECT: Mifepristone/Misoprostol

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Suzanne Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Med. Serv., Inc
1207 N. 200th., Suite 214
Seattle, WA 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
	3 bott. x 51 tabs	200mg tablets
	= 153 tabs	Mifepristone
		Lot # JMP2524-105
		Exp. 7/97

Suzanne T. Poppema, M.D.
Seattle, WA CRN 3032921
EI: 11/01/99-11/05/99
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SIGNATURE OF INVESTIGATOR

DATE

4/23/99

DATE

MIF 000653

April 26, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.
Dr ———— patients #30, #32, #35, and #37, Dr. Sheehan - patient #81,
Dr. Haskell - patient #158, and Dr. Mishell - patient #159.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ———— this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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April 6, 1995

Dr. Suzanne T. Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

Enclosed please find two copies of an Amendment to the contract between your study center and the Population Council for the above-referenced study.

Please have the appropriate person at your center sign both and forward them to ——— at the Council.

The Amendment is necessary since the original contract period has expired.

If you have any questions, please call.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 41 of 86

signed + sent 4/12/95

April 3, 1995

Suzanne T. Poppema, M.D.
Aurora Medical Services, Inc.
12-7 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

The IRB under the Auspices of ——————————— has been notified on your behalf by ——— of adverse events in the Population Council clinical protocol entitled: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days", (protocol #166A/B). Notifications have occurred on February 17, 1995, March 6, 1995, and March 14, 1995.

The above mentioned adverse events have been reviewed by the IRB. The IRB will continue to review these documents as necessary and ——— clinical study will continue to act as liaison on behalf of your clinic.

We look forward to continuing to work with you and your staff on this exciting project.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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March 22, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure working with you and your staff during my monitoring visit on March 14-16, 1995. I appreciate the time you and your staff allotted me to review the case report forms and medical records.

During this monitoring visit only one (1) previously monitored case report form was corrected, completed and retrieved. Also, during this visit the twenty-one (21) completed patient case books were monitored. All twenty-one (21) newly monitored case books were corrected and retrieved. Except for some minor corrections and the clarifications of some adverse event data, all of the case report forms and source documentation were found to be in excellent shape.

Data discrepancies from previously collected case report books were also addressed during this monitoring visit. All discrepancies were resolved and the case report forms corrected and returned to [redacted]

Unfortunately, during this monitoring visit two (2) protocol violations were noted. Both of these violations to the protocol were related to the entry of patients with a medical history of asthma. As stated in the protocol on page 7, asthma is an exclusion criteria.

Once again it was a pleasure to visit your clinic. If you have any questions or concerns, please do not hesitate to contact me.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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cc: [redacted]

March 16, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

Enclosed please find additional study medication (204 tablets) for the Mifepristone/Misoprostol Study.

Please sign and date the medication inventory form, photocopy for your files, and return to my attention in the enclosed self-addressed stamped envelope.

Thank you for your continued cooperation.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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March 1, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure working with you and your staff during my monitoring visit on February 6-9, 1995. I appreciate the time you and your staff allotted me to review the case report forms and medical records.

During this monitoring visit seven (7) previously monitored case report books (009, 016, 018, 019, 020, 021, 022) were corrected, completed and retrieved. Also during this visit an additional twenty-nine (29) new case books were monitored. Out of these twenty-nine (29) monitored case books twenty-six (26) CRFs were complete, corrected and retrieved. Except for some minor corrections and the clarification of some adverse event data, all of the case report forms and source documents were found to be in excellent shape. There were no protocol or procedural violations noted.

As a reminder, all patient diary cards are now being collected and the bleeding data entered into the database. A number of your patients have failed to return their diaries for various reasons. The diary is necessary for not just bleeding data but also this is the only record of concomitant medication and possible adverse events recorded outside of the clinic. Please emphasize to you patients that the diary is a very valuable tool for the collection of study data.

If you have any questions or concerns, please feel free to contact me at ———————

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 45 of 86

cc: ———————

February 2, 1995

Dr. Suzanne T. Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It has come to our attention that study coordinators/medical personnel have been contacted by individuals from the public relations offices of the Population Council. These contacts/questions have been with regard to patient enrollments etc. Interactions between your center's public relations group and this office at the Council are normal. However, due to the confidential nature of the study data information with respect to patient enrollment, adverse events or any medical aspects of the study, this information should only be conveyed to personnel who have been identified as such to you or the Council. If you receive any telephone or other contacts from individuals other than these, even if they identify themselves as being from the Population Council, please get a telephone number and notify either Dr. Ann Robbins at the Council, or me before you return a call.

Thank you in advance for your assistance. We all need to continue to work together to avoid any unwanted or unnecessary publicity regarding the study.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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February 2, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

You were recently informed by ——— that as part of our ongoing safety evaluation, the Population Council have requested additional information on patients who had serious adverse experiences and on patients who are treatment failures. We thank you for your cooperation in submitting the information on these patients to us in a timely fashion.

An additional request has been made by the Council. When summarizing the events of the adverse experience or treatment failure, the pre and post Hgb and/or Hct results, if available, should be included in your narrative. If the Hgb and/or Hct level was not done, please note this in your narrative. These results are required for all summaries submitted to date.

Additionally, please be reminded that all patients must return their study diary card. Photocopies of the diary card are being retrieved during the monitoring visits by the CRA and the bleeding information is to be entered into the database. Every effort must be made to ensure the return of the diary card.

Thank you for your continued cooperation and should you have any questions, please do not hesitate to contact me or ———

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99

PHONE CONTACT

BETWEEN: _____ (Aurora Medial Services)/

DATE: January 31, 1995

RE: Timeline of Study Completion

SUMMARY OF CONVERSATION

_____ contacted me today to obtain information on when this study will be completed. Dr. Poppema is interested in hiring additional help, and does not know how long the study will run. I informed _____ that although we only have nine enrolling centers at this time we are still actively involved in the recruitment process for additional centers. As of now, our goal is to complete the study by June, however this is dependent on if these additional centers become part of this multi-center trial. _____ felt confident that the hiring of an additional employee would be beneficial.

January 23, 1995

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure working with you and your staff during my monitoring visit on January 5, 1995. I appreciate the time you and your staff allotted me to review the case report forms and medical records.

During this monitoring visit the nine previously corrected case report books (patients 001-009) were retrieved Also during this visit an additional eight case books were monitored, corrected and retrieved. Except for some very minor corrections and the clarification of some adverse event data, all the case report forms and source documents were found to be in excellent shape. Enrollment continues to be brisk and there were no serious protocol or procedural violations noted.

I am glad to report that the deficiencies cited during the first monitoring visit have improved greatly. Patient follow-up for cessation of uterine bleeding after Day 15 of the study is now being documented within a reasonable time frame and the Investigator's Questionnaire was completed for most of the cases being reviewed.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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The one item that should be stressed with the office staff is reviewing the patient's symptoms and medications as listed on the patients' study diary. Please make sure that these patient diaries are reviewed during the visit and clarification of symptoms and adverse events (start and stop dates and severity) are documented clearly. Also, documentation of the drug relationship should be made in the clinic record as it relates to the adverse event.

Due to your sites steady and rapid enrollment, I have confirmed the week of February 6, 1995 for my next monitoring visit with ——— During this visit all outstanding completed case report books will be monitored, corrected and collected. All case report forms must be completed and signed.

Once again, it has been a pleasure working at this study site and I look forward to seeing you during the week of February 6, 1995. If you have any questions or concerns, please do not hesitate to call me at ————————

Sincerely,

TSP

[ ]

Aurora Medical Services Inc. PS

1207 North
200th Street
Suite 214

Seattle
Washington
98133

(206) 546-8891
FAX 546-9641

January 19, 1995

Irving Spitz, M.D.
The Population Council
1230 York Avenue
New York, New York, 10021

Dear Dr. Spitz,

Adverse event report:, Pt initials —— 050
DOB: 08-10-64
LMP: 11-18-95 Final Assessment of amennorhea: 62 days, Group 3
Hct on 1-11-95: 42%
mifepristone admin: 1-11-95 @ 15:47 600 mg.
Misoprostol admin: 1-13-95 @ 10:13 400 mg.
Discharged @ 14:15

1-13-95: Telephone call from pt c/o heavier bleeding than when here in our office, >3 pads per hour, and feeling dizzy. Advised patient to return to the clinic immediately, but because of rush hour traffic, she worried that it may take 11/2 - 2 hours. Because patient was feeling faint with sitting and standing, advised to go to Valley General ER close to home.

ER physician advised. Pt arrived with severe postural hypotension, BP 60/palpable, Hct 35% and vaginal bleeding. An emergency D&C was performed with decidua and villi removed. Post-operative Hct was 25% . Pt was sent home in the am. No transfusion was necessary.

Telephone follow-up with pt on 01-17-95 reported no significant bleeding and feels fine currently. She will return for her check-up in two weeks.

Principal Investigator:
Suzanne T. Poppema, M.D.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 51 of 86

MIF 000665
Reported by Pharmacia

January 12, 1995

Dr. Suzanne Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"
(Protocol 166A)

Dear Dr. Poppema:

I have recently joined ——— and am looking forward to working with you, the Population Council and the other members of our team on this exciting project.

As part of our ongoing safety evaluation, the Population Council have requested additional information on patients who had serious adverse experiences and on all treatment failures. They would like to receive this information on an ongoing (weekly) basis. To facilitate data collection we have designed the enclosed forms. We would appreciate your completing these forms and including all events that have occurred to date. Please send the completed form to ——— by facsimile.

In order to facilitate our overall review of the data on an ongoing basis we need the case report forms retrieved from all the sites as soon as possible. It would therefore be extremely helpful if you could ensure that the study coordinator has sufficient time available to complete the case report forms as the patient is enrolled in the study. At each visit the monitor may need to spend several hours with the study coordinator so that all corrections have been made before the case report forms leave the site. We would appreciate your confirming that this is feasible when the monitor schedules a site visit.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 ———
Exhibit 7 Page 52 of 86

Enrollment is proceeding very well thanks to the enthusiasm and efforts of you and your colleagues. I look forward to meeting with all concerned in the not to distant future.

/S/

[ ]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 53 of 86

January 9, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

Enclosed please find additional study medication (204 tablets) for the Mifepristone/Misoprostol Study.

Please sign and date the medication inventory form, photocopy for your files, and return to my attention in the enclosed self-addressed stamped envelope.

Thank you for your continued cooperation.

Sincerely,

[illegible]

[illegible] to send me photocopied in my name

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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PHONE CONTACT

BETWEEN: _____ (Dr. Poppema)/ _____

DATE: January 5, 1995

RE: Additional study drug

SUMMARY OF CONVERSATION

_____ alled to let us know they would need additional study drug before the first of the next week if possible. In addition, she made reference to an adverse event at the center which had been called into the Council. This was not communicated to us by the Council and will be followed-up.

Aurora Medical Services Inc, PS

1207 North
200th Street
Suite 214

Seattle
Washington
98133

(206) 546-8891
FAX 546-9641

January 3, 1995

Irving Spitz, M.D.
The Population Council
1230 York Avenue
New York, New York, 10021

Dear Dr. Spitz,

Adverse event report: Pt initials —— 33
DOB: 12/16/71
LMP: 11/2/94 Final assessment of amennorhea: 52 days, Group 2
Hct on 12/21/94: 39%
mifepristone admin: 12/21/94 @ 10:45 600mg.
Misoprostol admin: 12/23/94 @ 09:00 400 mg.
U/S p4hrs : no sac seen but blood and tissue still in uterus.

12/29/94: Call from pt @10:00 AM c/o heavy bleeding for 3 hrs without sx of dizziness or cramping. Advised to take methergine, 0.2mg q 4hrs and to call back if no decrease in bleeding 1hr after methergine. Call from pt's mother @11:45 saying pt still bleeding heavily; advised to bring pt in immediately. Call from pt's mother @12:00 stating pt had syncopal episode and emergency ambulance called. Call from EMT @12:15 stating pt BP of 80 and P 126 with heavy vaginal bleeding and pallor. EMT decision pt too unstable to bring to office so taken to Group Health ER(pt member of this HMO).

I spoke with ER and advised him of the situation and of pt's participation in the M/M study.

Call to ER @ 16:00 pt seen and found to have postural signs of acute blood loss, heavy vaginal bleeding, and Hct of 24%. The patient underwent an emergency suction and her bleeding stopped. She was discharged from the acute care unit that evening in stable condition. Telephone follow/up on 12/30/94 found the patient stable, with no significant bleeding, and feeling fine. She never received a blood transfusion and will return as scheduled for her 2 week check. She was prescribed iron and Doxycycline.

Principal Investigator:
Suzanne Poppema, MD

December 14, 1994

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

It was a pleasure once again to visit you and your staff on my last monitoring visit on November 30 and December 1, 1994. I appreciated the time you and your staff allotted me to review the case report forms and medical records.

During this visit nine (9) case report forms of the twenty-one (21) patients entered into the study were reviewed. Except for some minor corrections, the medical records, case report forms and source documents were found to be in excellent shape. Enrollment has been brisk and there were no serious protocol or procedural violations noted. On the other hand, there are two areas of concern that need to be addressed.

First is the lack of follow-up on the patients that continue to present at Day 15 with uterine bleeding. Although an actual office visit is not necessary, the "cessation of uterine bleeding" should be documented in the clinic charts and case report forms in a timely manner. The reason for the timely telephone contact is to also capture any persistent symptoms or possible adverse events that may have occurred since the last visit. Concomitant medications should also be captured for this time period.

Secondly, the Investigator's Questionnaire needs to be completed for each patient. Not only are we interested in the principal investigator's opinion of the medications involved, but this page, more importantly, serves as the final evaluation and verification of the patients status in the study.

To clarify the question your staff asked regarding adverse events, please follow these guidelines for recording AEs into the case report forms. If an adverse event's severity or drug relationship should change, these adverse events should then be listed as new events recorded with a new start date, and/or new severity or drug relationship. All symptoms recorded during the 4 hour observation period still are not included on the adverse event page unless they continue beyond the 4 hour observation period. Also any symptoms listed on the patients diary should be recorded as adverse events, and only excessive bleeding will be considered an adverse event. Because the patient's diary does not address severity of pain/cramps in the section titled "Menstrual Symptoms", the patient should be questioned about the severity during the clinic visit. This should be documented in the clinic notes.

During the four hour observation period following the administration of the misoprostol the question regarding "Time of expulsion" should be based on the care givers assessment of the patients symptoms.

If you have any questions please do not hesitate to contact me at [redacted] I wish you continued success with this study and will plan a monitoring visit with you probably the second week of January.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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December 7, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"

Dear Dr. Poppema:

With regard to the weekly update forms which were used last week for the above-referenced study, please utilize the following definitions: (Attached is the newly revised form. Please disregard all previous forms).

Column 1 - Patients enrolled in the group for that week.

Column 2- Total abortions for the group in that week regardless of mode. Thus both surgical and medical abortion data are collected.

Column 3 - Complete medical (M&M) abortions in the group for that week.

For example: for a particular week in group 1 (≤ 49 days). Lets say 5 patients enroll, there are 2 surgical procedures, regardless of when the subjects enrolled, and there are 4 medical successes. The data would be recorded as:

Enrolled	Total Abortions	Complete Medical Abortions
5	6	4

Giving a 67% success rate for that group that week.

If you have any questions please call your CRA, _____ or me.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 59 of 86

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FAX TRANSMISSION

EVERY FRIDAY

ATTN: _____ AT: _____

FAX: _____

MIFEPRISTONE/MISOPROSTOL
WEEKLY PATIENT UPDATE

DR. SUZANNE POPPEMA

Week Ending: _____

GROUP 1 ≤49			GROUP 2 50-56			GROUP 3 57-63		
Total Enrolled	Total # of abortions surgical and/or medical	Complete Medical Abortion	Total Enrolled	Total # of abortions surgical and/or medical	Complete Medical Abortion	Total Enrolled	Total # of abortions surgical and/or medical	Complete Medical Abortion

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 60 of 86

FAX TRANSMISSION SHEET

DATE: 12/5/94

TO: [redacted] **AT:** Denver Med -

FROM: [redacted] **AT:** _____

REFERENCE:

POPC Study.

ADDITIONAL COMMENTS:

FYI - some clarifications for recording values in the case report form -

Number of pages (including transmittal): 2

Our Fax Number is: _____

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99

POPULATION COUNCIL STUDY UPDATE

CRF Clarifications

Page 3 (Crown-Rump length)

If the ultrasound result shows the length of crown-rump as 13 mm it should be recorded on the CRF page as 13.0 mm not 013 mm

Page 12

When a serious adverse event (SAE) is reported by a study center and in turn reported to the FDA via a MEDWATCH Form, this adverse event also needs to be captured on the CRF. All SAEs occurring during the study will be copied to each CRA. If during a monitoring visit, it is noted on the AE page under "Action Taken" that a patient was hospitalized and you do not have a copy of the SAE, please alert me ASAP. Any overnight hospitalization will need to be reported to ——— nd the Population Council.

"Excessive Bleeding" being captured as an adverse event is defined as: Bleeding that saturates one sanitary napkin every hour for three consecutive hours.

Administrative:

Corrections can be made to a CRF page after the final date of signature of the investigator. However, if there is something added to the CRF that is medically substantive, the Investigator should re-sign the page.

November 30, 1994

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"

Dear Dr. Poppema:

Recent discussions with the Population Council have prompted a change in the reporting structure of patients enrolled weekly at your center.

Attached is a revised patient update form to be faxed to ——— very **Friday**. Please destroy the previous version. Field #1 (total enrolled) has been modified from cumulative patient enrollment to the number of patients enrolled during that week **only**. Field #2 (total evaluated) is the number of patients who have completed the study (ie through Day 15) during that week. Field #3 (complete abortion) is the number of patients who have aborted during that week due to the ingestion of mifepristone and/or misoprostol up to Day 15. This form is designed to capture the identical information for each group.

Since complete abortion status has not been requested previously, please provide this information for all groups, broken down weekly, at the bottom of this form with the December 9, 1994 fax.

Should you have any questions, please contact me or the CRA responsible for your center.

Sincerely,

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Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 63 of 86

FAX TRANSMISSION

EVERY FRIDAY

ATTN: _____ AT: _____

FAX: _____

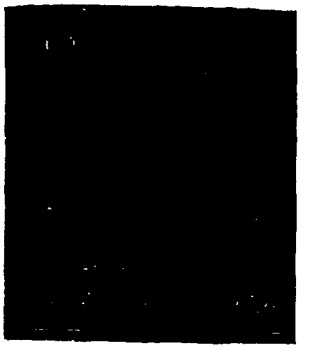
MIFEPRISTONE/MISOPROSTOL
WEEKLY PATIENT UPDATE

DR. SUZANNE POPPEMA

Week Ending: _____

GROUP 1 ≤49			GROUP 2 50-56			GROUP 3 57-63		
Total Enrolled	Total Evaluated	Complete Abortion	Total Enrolled	Total Evaluated	Complete Abortion	Total Enrolled	Total Evaluated	Complete Abortion

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 64 of 86



November 22, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suire 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"

Dear Dr. Poppema:

Effective November 22, 1994 there will be a new contact procedure in the event of a serious or unexpected Adverse Event. Please contact:

The Population Council
(1- 800- 327-8730)

This number is a 24 hour/day number.

Sincerely

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Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 65 of 86

November 18, 1994

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 North 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Enclosed please find one hundred (100) Non-Participant Patient Questionnaire Forms. As discussed at the Investigator Meeting on October 3 & 4, 1994, this form is to be completed for all patients who come to your center and are offered the possibility of trying the medical abortion method and are not excluded by study criteria but decline to participate at any point prior to signing an informed consent.

Should a patient refuse to answer these five questions, please write on the form that the patient refused to answer. The screening number on each form is assigned sequentially. This will provide us information on the number of patients who came to your clinic and were given the choice of surgical vs. medical abortion.

Please retain a file for these forms as they will be reviewed and photocopied at each monitoring visit.

Should you have any questions on the use of this form, please contact me directly.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 66 of 86

November 18, 1994

Suzanne T. Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A)

Dear Dr. Poppema:

It was a pleasure meeting you and your staff during the initiation of the Mifepristone/Misoprostol study at Aurora Medical Services on November 8, 1994. The time allotted from your busy day for this meeting was appreciated.

During this meeting both the protocol and a copy of the case report form were reviewed. Inclusion/Exclusion criteria were reviewed in detail with special emphasis on calculating days of amenorrhea, uterine size based on pelvic examinations and the results of the transvaginal ultrasound for proper patient grouping.

Dosing and study procedures were reviewed for the study. Source documentation and the implementation of a special clinic progress note were discussed with ————————

The minutes from the Investigator's Meeting on October 3-4, 1994 were reviewed for clarification of: redosing of mifepristone and/or misoprostol within 15 minutes of vomiting, if occurred, the use of the Robinson Scale, and the administration of misoprostol 36-60 hours after the mifepristone.

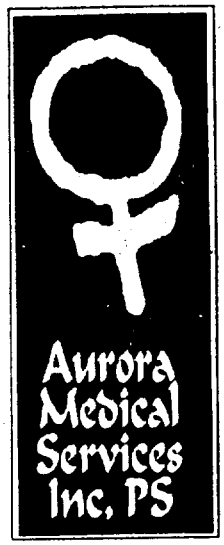
The regulatory documents were reviewed with ——— and a new FDA Form 1572 was signed due to the addition of ———————. The following documents still remain outstanding:

- Signed 10/13/94 protocol page
- CV of Director at ——————— requested 11.21.94
- Confirmation letter acknowledging that you are aware that the Justice Department was informed of your participation in this trial

If you have any questions please do not hesitate to call me at ————

Sincerely,

/S/



November 8, 1994

Dr. Irving Spitz
The Population Council
1 Dag Hammarakjold Plaza
New York, New York, 10017

1207 North
200th Street
Suite 214

Seattle
Washington
98133

(206) 546-8891
FAX 546-9641

Dear Dr. Spitz,

I received your letter today concerning your notification of the Justice Department of our participation in the mifepristone trial. We appreciate the added safety this affords our clinic.

Yours Sincerely,

Suzanne T. Poppema, M.D.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
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Faxed 11.8.94
12.7.94

The Population Council

Center for
omedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

November 8, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

We are pleased that you will be participating in the mifepristone/misoprostol study. The Justice Department have requested a list of clinics where this study will be conducted. They wish to alert federal marshalls in your area of this trial. This will allow federal marshalls to respond to any potential call for help. We have notified the Justice Department that your clinic will be participating in this study.

If you should have any further queries or questions, please do not hesitate to contact me. Please acknowledge receipt of this letter.

Thanking you.

Yours very sincerely,

/s/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 76 of 86

FAXED
11-8-94

FAX TRANSMISSION SHEET

DATE: 11/8/94

TO: [redacted] AT: [redacted]

FROM: [redacted] AT: [redacted]

REFERENCE:

Re: Letter from Dr. Spitz (PapC.)

ADDITIONAL COMMENTS:

Hi

Dr. Spitz sent Dr. Poppema a letter informing her that the Justice Department is knowledgable of her participation in the M+M trial. Please have Dr Poppema write a letter confirming receipt of this. Please send or fax this letter to

Number of pages (including transmittal): (1)

Our Fax Number is: [redacted]

Thankyou

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 71 of 86

November 2, 1994

Suzanne T. Poppema, M.D.
Aurora Medical Services, Inc.
1207 North 200th Street, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol 166A)

Dear Dr. Poppema:

This letter is to confirm my visit to your site to initiate the above mentioned study on Tuesday, November 8, 1994 at 7:30 AM.

During this initiation visit the protocol will be reviewed along with the minor changes which have occurred since the investigators meeting. Also, the case report forms will be reviewed to assure proper data entry. All study drug will be hand carried to your site.

It would be most helpful if all of the sub-investigators and study nurses involved in the study would be present for this meeting.

If you have any questions, please do not hesitate to call me at _____

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 72 of 86

November 1, 1994

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" Protocol 166A

Dear Dr. Poppema:

In recent discussions with the Population Council, it was determined that an addendum be added to the Investigator Agreement to clarify the clause in the contract regarding publishing rights. This addendum is enclosed for signature and should be returned to my attention at your earliest convenience.

If you have any questions or concerns, please feel free to contact me.

Sincerely,

/s/

[ ]

send + faxed 11/2

ADDENDUM TO INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol: " Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days".

Protocol No. 166A, and agree to conduct the study as outlined herein.

This study is a joint project between Aurora Medical Services, Inc. and The Population Council, Inc. Individual investigators may only publish their own center's data following acceptance of the manuscript(s) with the overall trial results. Any publication from an individual investigator must make a reference to the publication(s) with the overall results and the manuscript must be sent to The Population Council, Inc. prior to submission for publication. The monitoring agency for the clinical trial will provide each investigator a summary of the data from his/her clinic.

11-2-94
Date

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 74 of 86

October 20, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: Evaluation of the Efficacy, Safety and" Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"

Dear Dr. Poppema:

Please find enclosed a copy of the informed consent that was approved by ——— .RB on October 12, 1994

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 75 of 86

October 18, 1994

Dr. Suzanne Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Enclosed please find the final revised protocol entitled "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days" dated October 13, 1994. The original draft protocol you received, dated July 15, 1994 has now been modified twice; first on September 6, 1994. This protocol was reviewed in New York at the Investigator's Meeting. This final version dated October 13, 1994 encompasses all changes suggested at that meeting. If you did not retain a copy of the September 6, 1994 protocol along with the page outlining the changes from July 15, 1994, please let us know since the changes outlined with this October 13, 1994 document attached to the protocol reflect those made to the September 6, 1994 text only.

Because the overall trial is being conducted as two identical trials, centers are being classified with an identifier of either A or B. Your center will carry the identifier of (A) and this is reflected on the protocol and informed consent. This technical change should be part of your letter to the local IRB chairperson.

Your local IRB must receive both sets (September 6th and October 13th) of changes if they approved the July 15, 1994 copy of the protocol. Likewise, if your center is utilizing a local IRB, the informed consent must be revised to contain both sets of changes as well.

Once approval is obtained, please forward the IRB approval letter for the protocol and informed consent along with a copy of the revised informed consent to

Additionally, if you modify the informed consent in any way from that contained in Appendix I of the protocol, you need to attach a detailed outline of the changes to the informed consent.

The Council has requested that all informed consents contain the title and date of the protocol as an identifier on EACH page of the informed consent.

Once these documents are received, an initiation visit can be scheduled (provided contracts, proof of insurance and budgets are in place). All center's using ——— IRB received IRB approval on October 12, 1994.

Although advertising is not recommended, please be reminded that if you choose to advertise, it MUST be approved by the IRB prior to its implementation. The advertisement and IRB approval of this advertisement must be sent to ———

We are in the process of finalizing your regulatory package for submission to the FDA. ——— your CRA, will contact you shortly to request outstanding documents.

Should you have any questions, please feel free to contact me.

Your continued cooperation is appreciated.

Sincerely,

———

October 7, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days

Dear Dr. Poppema:

It was a pleasure to meet you in New York during the Mifepristone/Misoprostol Investigator's Meeting and it is exciting that the US clinical trial is about to begin.

We are in the process of amending the protocol, informed consent and case report form. The amended protocol and informed consent will be sent to you shortly for submission to your IRB. This submission should be able to undergo expedited review. Once the approval letter is received at ——— we can arrange for a site initiation visit and drug shipment. For the centers using ——— IRB this amended protocol will be submitted for the October meeting.

Now that all the study centers have been selected for participation, please be informed that the Clinical Research Associate (CRA) assigned to your center is ——— He will contact you or your study coordinator shortly to introduce himself and arrange to initiate the study. We anticipate to begin by the last week of October. Once this initiation occurs, patients can be enrolled. This initial enrollment can be a time of hecticness and various questions may need to be answered to ensure protocol adherence. For this initial time period, please contact me directly at ———, protocol consistency can be maintained at all study locations. In my absence, please feel free to speak with ——— Once the study progresses, your Clinical Research Associate will become your primary source for information.

Thank you for your participation at the meeting. ——— looks forward to finalizing all business agreements and to a successful collaboration on this exciting project.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 78 of 86

FAXED
9-26-94

Poppema

FAX TRANSMISSION SHEET

DATE: 9/26/94

TO: [redacted] **AT:** [redacted]

FROM: [redacted] **AT:** [redacted]

REFERENCE:

Mifepristone

Investigator's meeting

ADDITIONAL COMMENTS:

Please find the agenda for the mifepristone Investigator's meeting being held on October 3-4, 1994

Number of pages (including transmittal): 2

Our Fax Number is: [redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921

D R A F T

MIFEPRISTONE INVESTIGATOR'S MEETING OCTOBER 3-4, 1994

AGENDA

October 3, 1994

TIME	TOPIC	SPEAKER(S)
8:30 - 9:00	Continental Breakfast	
9:00 - 9:30	Project Background	Population Council
9:30 - 11:30	U.S. Protocol	Population Council
11:30 - 12:30	European Experience (A. Ulmann)	[redacted]
12:30 - 1:30	Lunch	
1:30 - 2:30	U.S. Pilot Study	
2:30 - 3:30	Transvaginal Ultrasound	
3:30 - 4:30	Mechanics of the Protocol	Population Council
	General Discussion	

October 4, 1994

TIME	TOPIC	SPEAKER(S)
8:30 - 9:00	Continental Breakfast	
9:00 - 10:00	Monitoring and Analysis	Population Council
10:00 - 10:45	Public Information/Media	[redacted]
11:15 - 12:00	Legal Issues	
12:00 - 12:45	Security/Defense	
12:45 - 2:00	Lunch	
2:00 - 4:15	Case Report Form	Population Council
4:15 - 5:00	Wrap Up	Population Council
	General Discussion	

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 80 of 86

September 22, 1994

Dr. Suzanne T. Poppema

Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days" (Protocol #166 A)

De? ———————

On behalf of the Population Council, we would like to invite you to an Investigator's Meeting on Monday and Tuesday, October 3 and 4, 1994 at Rockefeller University in New York. This meeting will begin at 8:30 AM on Monday for discussion of the overall project, protocol, the European Experience, case report forms, and the initiation of all study sites. Prior to this meeting, all regulatory documentation, budget grids and contracts should be submitted to ———————— for a timely study start-up. All travel arrangements, if not already done should be made through ————————————————

Please contact ————o inform her of the name each person at your site attending the meeting if hotel room accommodations are necessary. ——— as reserved a block of rooms at the ————————————————The investigator and study coordinator from each center are invited. At the end of the meeting a reimbursement form will be provided to cover out of pocket expenses such as cab fare, etc. If more than (2) representatives are interested in attending, please contact ———————— or prior approval.

In addition, you will find enclosed a copy of a letter from ————. the Council, regarding security measures and public relations. Please review these materials.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 81 of 86

I have also enclosed a copy of the final study protocol and prototype Informed Consent, as well as a page identifying changes from the earlier version. There should be no need for a full IRB review of the changes. Additionally, I have included a copy of the CRF being used in the pilot study for your review.

Should you have any questions, please contact me at ———

Sincerely,

/S/

———

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 ——
Exhibit 7 Page 82 of 86

September 21, 1994

Executive Diretor
Aurora Medical Services
1207 North 200th Street Suite 214
Seattle, WA 98133

Dear ———

Thanks for your time on the telephone earlier today. As we discussed, I have enclosed the following items for the upcoming trial with mifepristone:

Business Agreement

Two copies of the business agreement for the study are enclosed for your review. Please have Dr. Poppema review the document and sign both copies where indicated; then return both copies to my office via Federal Express. I will forward copies to the Population Council for signature and return a fully executed copy to you.

Patient Consent Form

I have also provided a copy of the suggested consent form with the contact persons and phone numbers for your center included. Please review the form and note any corrections or changes which you feel are required. If agreeable, this form will be submitted to the IRB with your regulatory documents.

Additionally, we will need to receive a copy of Dr. Poppema's CV within the next week or so. As always, please feel free to call with any questions or concerns. I look forward to seeing you in New York and to a successful collaboration on this exciting project.

Sincerely,

/S/

August 19, 1994

Suzanne Poppema, MD

Aurora Medical Services, Inc. PS
1207 North 200th Street
Suite 214
Seattle, WA 98133

Dear Dr. Poppema and

It was a pleasure to meet you both earlier this week when I visited Seattle to discuss the Population Council clinical trial which will study the use of mifepristone/misoprostol as an abortifacient. I appreciate the opportunity to meet your staff and to tour the clinic facilities.

As we discussed, the Council has selected your center to participate in the upcoming trial with mifepristone pending suitable contractual and budgetary agreements. As the clinic facilities appear more than adequate for the study, I would suggest that we concentrate on the following items in preparation for the beginning of the trial this Fall:

1. *Curricula Vitae* for all investigators to be involved in the trial.

2. *Laboratory normal values* observed by you for hematocrit and hemoglobin levels.

3. *Request for IRB approval*
As the trial will be conducted at your private clinic, regulations permit you to apply to any duly constituted Institutional Review Board for approval to participate in the study. We convene such an IRB at ——— which would be happy to receive your request for review and approval; thus I will ask that you submit a brief letter requesting permission to participate in the study to the IRB chairman:

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 84 of 86

MIF 000698

On your behalf, I will provide your CV, those of your colleagues, your consent form and a report on the clinic facilities for review by the committee.

4. *Research Contract/Budget*
Please review the draft contract which we discussed during our meeting and provide any comments on the language of the agreement. After your legal counsel has provided comments/feedback, we can finalize the document for signatures by the Council and yourself. In addition, we will need a completed budget grid and proof of insurance as noted in the research contract.

As we discussed, the Council plans to begin the trial in mid-October and an investigators' meeting is scheduled for _____. We will be in touch to assist with trvel arrangements and to confirm the names of those who will attend from your center.

Once again, thank you for your warm hospitality during my visit. Please feel free to call with any questions or concerns - we look forward to a successful collaboration on this exciting project.

Sincerely,

[signature]

c:

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 85 of 86

August 11, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

It was a pleasure speaking with you today regarding the Population Council protocol which will study the use of mifepristone/misoprostol as an abortifacient. I have enclosed a copy of the study protocol and ask that you review the document so that we might further discuss the possibility of placing the trial at your center.

As we discussed, our plan is to visit potential study centers during August and September for 'pre-study' visits to tour the facilities and meet research staff members. During that meeting, I would like to review the study protocol and discuss any questions or concerns which you might have regarding the proposed study procedures.

In addition, I have enclosed an investigator brochure and a budget estimate form for your use. At this time, we will ask that you itemize your fees in the areas outlined on the form so that an overall budget for the trial can be estimated. I look forward to seeing you on August 16, 1994 and plan to arrive at your office at 1:00 PM. Thank you again for your time and interest in this study.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 7 Page 86 of 86