Electronic Mail Message

Date: 9/11/00 9:44:00 AM
From: [redacted]
To: See Below
Subject: Re: URGENT Re: Mifepristone Label!

Please ignore my last message. We were able to get into [redacted] e-mail.
Sorry to have bothered you.

[redacted]

To: [redacted]
To:
To:
To:

Electronic Mail Message

Date: 9/11/00 9:41:07 AM
From:
To:
Subject: - no subject (01JU1J79XW4S94DQQE) -

Printed by

Electronic Mail Message

Date: 11-Sep-2000 09:09am
From:

Dept:
Tel No:

TO:
TO:

CC:
CC:
Subject: Call List

OWH was asked to prepare a telephone call list. Here is a list of key women's groups. We are checking our names, phone and fax numbers. I will get it to you this afternoon.

This list does not include health professional organizations. We will send that list seperately.

RU486

Women's Groups

DHHS/OWH

The Feminist Majority

Planned Parenthood Federation of America

National Abortion Rights Action League

National Organization for Women

NOW Legal Defense and Education Fund

Partnership for Women and Families

National Women's Law Center

American Association of University Women

Society for Women's Health Research

National Council of Negro Women

MANA (Mexican American women)

La Raza

National Congress of American Indians

HADASSAH

National Council of Jewish Women

National Asia/Pacific Island Women's Health Organization

Disability Rights Education and Defense Fund

Jacobs Institute

Alan Guttmacher Institute

Business and Professional Women

Washington Business Group on Health

National Right to Life
Laura Echeevarria, Director
T:(202)626-8800
F:(202)347-3119

Christian Coalition of America
Pat Robertson, President
T:(202)479-6900
F:(202)479-4260

Feminists for Life
Serrin Foster, President
T:(202)737-FFLA
F:(202)737-0410

Americans United for Life
Clark Forsythe, President
T:(312) 492-7234
F:(312) 492-7235

Electronic Mail Message

Date: 9/8/00 9:29:00 PM
From:
Subject: RE: Mifepristone label and durg interactions

Thanks for this labeling suggestion. I'm okay with it.

Electronic Mail Message

Date: 9/7/00 5:16:09 PM
From: [redacted]
Subject: BCC:OPDRA Action Item following Pop Council meeting today

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 9/7/00 11:17:33 AM
From:
To: See Below
Subject: Inquiries on Mifepristone Application from HHS

I've been informed that all inquiries from the Department on this application should be forwarded to the office of the commissioner, attention Dr. Henney or

If you have any questions, please let me know.

To:
To:
To:
To:
To:
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To:
To:

Electronic Mail Message

Date: 9/5/00 3:19:41 PM
From:
To:
Subject: FWD: In re: RU-486

Another RU-486 e mail.

Electronic Mail Message

Date: 9/5/00 4:28:49 PM
From: [redacted]
Subject: BCC:questions regarding to your survey

Electronic Mail Message

Date: 8/30/00 6:11:14 PM
From:
To: See Below
Subject: Information letter to Population Council sent today

The Information Request Letter to Population Council was sent today. It included our attachments of the Medication Guide and revised Exhibit E of the proposed distribution system (Prescriber Agreement and Order Form).

The WORD.doc is attached to this email for your information. This letter was faxed to Pop Council and to Nancy Buc this afternoon.

Nancy Buc indicated that sponsor intends to respond to ALL the outstanding issues in their submission, likely on Tues. Sept. 5.

Thanks for all the prompt responses and reviews,

To:
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E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Aug-2000 05:50pm EDT
From:
Dept:
Tel No:

Subject: Re: More on Mifeprex Medication Guide

I think health care provider since there will be a lot of non-docs.

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Aug-2000 06:12pm EDT
From:

Dept: HFD-42 PKLN 17B17
Tel No:

TO:

Subject: FWD: Re: More on Mifeprex Medication Guide

FYI

Electronic Mail Message

Date: 08/28/2000 1:39:48 PM
From:
To: See Below
Subject: Health Daily News FYI mifepristone info

Searle Misopristol Pregnancy Reminder Issued As RU-486 Action Nears

Searle issued a reminder to doctors stating that its gastric ulcer treatment Cytotec (misoprostol) is contraindicated for use in pregnant women.

Searle sent its "important drug warning concerning unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labor or abortion" to physicians Aug. 23, about one month before FDA action is expected on a pending NDA for the abortifacient mifepristone.

The Population Council's RU-486 calls for a regimen of 600 mg mifepristone (three 200 mg tablets) followed two days later by 400 mcg of misoprostol. The group expects FDA action on the mifepristone NDA by Sept. 30.

Searle's "Dear Health Care Provider" letter states that "Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion." Cytotec is indicated for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers.

The company said it "has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy."

The letter was drafted in collaboration with FDA, the agency indicated. MedWatch data was used to collect information regarding adverse event reports, FDA said.

"Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain," Searle's letter explains.

In the letter, Searle (now part of Pharmacia) distances itself from the connection between Cytotec and its potential use in combination with misoprostol, noting that although "the uterotonic effect of Cytotec is an inherent property" of the prostaglandin product, "Cytotec is not approved for the induction of labor or abortion."

"Searle promotes the use of Cytotec only for its approved indication," the letter states. The letter also emphasizes that the company has not and does not plan to conduct trials of Cytotec as an aid to abortion.

Searle "has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it used for such purposes," the letter says.

In France, where mifepristone has been available since 1989, the Ministry of Health directed Searle to change Cytotec labeling, which included a contraindication for use in pregnant women, to allow for its administration to pregnant women in specialized hospitals.

After a positive advisory committee review of mifepristone in July 1996, FDA said it planned to meet with Searle to discuss a possible labeling change. FDA indicated that a Cytotec labeling change continues to be a possibility and will likely be discussed as part of the RU-486 review.

Searle's reminder to physicians, which emphasizes the "known and unknown acute risks to the mother and fetus" associated with misoprostol use, suggests the company may be opposed to changing the contraindication.

Mifepristone has been "approvable" since September 1996. The application has suffered delays due to difficulties retaining a manufacturer. A second "approvable" letter issued in February addressed labeling, manufacturing/chemistry and distribution issues, the Population Council said.

To:
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To:

Electronic Mail Message

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Electronic Mail Message

Date: 8/23/00 2:01:02 PM
From:
Subject: status of mifepristone protocol

H

I'm following up on the planned submission of the mifepristone protocol.

Any word on when OPDRA will be receiving this piece of information?

We are ready to proceed as soon as the protocol gets here.

Please keep me in the loop.
Thanks,

Electronic Mail Message

Date: 8/23/00 5:12:08 PM
From:
Subject: Re: status of mifepristone protocol

We are having a tcon with the sponsor and our Statistician on Fri. re. our estimation of sample size for the referral vs. nonreferral study. I know they are actively working on their proposal(s) for the Phase 4 studies. I will definitely keep you posted and immediately bring you any information I have from sponsor re. these protocols.

I should have a more definite idea re. when they plan to submit from our Fri tcon.

Hi
>
>I'm following up on the planned submission of the mifepristone protocol.
>
>Any word on when OPDRA will be receiving this piece of information?
>
>We are ready to proceed as soon as the protocol gets here.
>
>Please keep me in the loop.
>Thanks,

Electronic Mail Message

Date: 8/21/00 8:49:01 AM
From:
To:
Subject: FWD: RU 486 Approval

Another RU-486 e mail.

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 8/1/ 2000	DUE DATE: 9/ 5/ 2000	OPDRA CONSULT #: 00-0203

TO:

[redacted]
(HFD-580)

Division of Reproductive and Urologic Drug Products

THROUGH:

[redacted]
Project Manager
(HFD-580)

PRODUCT NAME: Mifeprex (mifepristone tablets) **NDA #:** 20-687	**MANUFACTURER:** Population Council

SAFETY EVALUATOR: [redacted]

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Mifeprex. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will ~~monitor~~ this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

for Medication Error Prevention

Office of Post-Marketing Drug Risk Assessment
Phone
Fax: (

Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Teleconference Minutes

Date: September 25, 2000 **Time:** 3:50 – 4:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Labeling

Meeting Chair: [redacted]

External Lead: Nancy Buc, Buc and Beardsley

Minutes Recorder: [redacted]

FDA Attendees:

[redacted] Office of Evaluation III (ODEIII; HFD-103)
[redacted] Project Management Staff, DRUDP (HFD-580)

Meeting Objective: To discuss the Package Insert for this product.

Discussion:

- in the last paragraph, on page 11, the sentence should be revised to read as follows " after exposure during the first trimester period"
- it is acceptable to delete in the **WARNINGS** and **INDICTIONS** sections, [redacted] (p. 5) and [redacted] p. 6)

Action Items:

- Nancy Buc will discuss these recommendations with Population Council and respond via fax followed by hard copy with revised labeling if acceptable

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

APPOINTMENT DETAILED
14-Sep-2000 to 14-Sep-2000

Date: Thursday, 14-Sep-2000 Time: 01:00pm Length: 01:30 Hrs:Min

Subject: NDA 20-687/T-Con Loc: #PKLN_17B43

Attendees

#580MEETINGS,

Agenda

NDA 20-687
Mifepristone
Population Council

This meeting is to discuss the label, exhibit E of the distribution system, and maybe the Phase 4 protocols. Please come prepared to discuss. I will forward the label and Phase 4 protocol suggestions we sent 9-13-00.

APPEARS THIS WAY
ON ORIGINAL

Key to Attendee Status

Bold = Confirmed Underline = Rejected All Others = Pending

Calendar Manager 14-Sep-2000

Teleconference Meeting Minutes

Date: September 14, 2000 **Time:** 1:00 – 2:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair: [redacted]

Minutes Preparer: [redacted]

FDA Attendees:

[redacted] Office of Evaluation III (ODEIII; HFD-103)
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
[redacted], Division of Drug Review and Evaluation II (DDREII; HFD-440)
[redacted] Regulatory Health Project Manager, DDREII (HFD-440)
[redacted] Regulatory Management, DDREII (HFD-440)
[redacted], DDREII (HFD-440)
[redacted] Project Management Staff, DRUDP (HFD-580)
[redacted] Regulatory Project Manager, DRUDP (HFD-580)

External Lead: Nancy Buc

Meeting Objective: To discuss the Information Request Letters sent September 13 and 14, 2000.

Discussion:

Labeling

- the Agency accepts the manner in which the sponsor is using the trademark symbol and the capitalization of the name "Mifeprex"
  - all CAPS and ™when used for the first time in any document
  - the second appearance the first letter capitalized with the trademark and an asterisk indicating the trademark belongs to Danco
  - anytime after that it will be first letter capitalized with the asterick
- the sponsor is reviewing the addition of the phrase "with a terminal half-life of 18 hours" and the addition of acid in the first sentence in the Distribution section of the label
- the sponsor agrees to the removal of the section on [redacted] in the **WARNINGS** section of the label

APPEARS THIS WAY
ON ORIGINAL

- in the **PRECAUTIONS** section of the label, the sponsor will respond to the elimination of the phrase [redacted] and replaced with "qualified physician"
- in the **PRECAUTIONS** section, Information for the Patient subsection [redacted] has been deleted
- replaced **PATIENT INFORMATION** with Medication Guide wherever it is used throughout the label
- in the **PRECAUTIONS** section, Drug Interaction subsection, the sponsor agrees with the deletion of the first paragraph and the replacement wording provided for by the biopharmaceutics reviewer
- in the **PRECAUTION** section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, the sponsor agrees to the change of the word [redacted] to genotoxic and also the elimination of sentence [redacted]
- in the **PRECAUTIONS** section, Teratogenic Effects subsection, heading Human Data, the sponsor will provide the Agency with the correct numbers of patients since May 2000, and agrees with the number changes the Agency made
- the sponsor agrees with the changes made to Table 2 to update the numbers
- in the **OVERDOSAGE** section the sponsor will provide the Agency with a reponses to changing the [redacted]" to "acute lethal dose"
- in the **DOSAGE AND ADMINSTRATION** section the sponsor will change the last sentence to match bullet number 3 of the **PHYSICIAN AGREEMENT**
- in the **DOSAGE AND ADMINSTRATION** section, Day One: Mifeprex Administration subsection should read as follows: "Patient must read the Medication Guide and read and sign the PATIENT AGREEMENT"
- in the **DOSAGE AND ADMINSTRATION** section, Day 3 : Misoprostol Administration subsection, the sponsor agrees to the suggested changes in both paragraphs
- in the **DOSAGE AND ADMINSTRATION** section, Day 14: Post-Treatment Examination subsection, the sponsor agrees with the proposed changes
- in the **HOW SUPPLIED** section the sponsor agrees with the proposed changes

PATIENT AGREEMENT

- the sponsor was not prepared to discuss the changes faxed to them in the September 14, 2000 Information Request letter

ORDER FORM

- the sponsor agrees to the addition of a date line for the date of signature

PRESCRIBER AGREEMENT

- the sponsor agrees with the addition of the numeric digits following the "1-877-4 Early Option" phone number
- the sponsor agrees with the change of [redacted] to "administration" in the last paragraph
- the sponsor will add the distributors name, address, phone number, fax number, and website to the end of this document

Phase 4 Commitments

- the sponsor needed clarification of the term "Emergency intervention"; the Agency defined it as medically necessary intervention (i.e. heavy bleeding)
- the sponsor will need to respond with the commitment to perform the Phase 4 studies in a submission to the NDA
- [redacted]

- the sponsor will need to address adding the language from the most recent European label as a contraindication for inherited porphyria in the label

Action Items:

- the sponsor must to submit the revised label, agreement to Subpart H, and the commitment to perform studies
- meeting scheduled for September 15, 2000 at 11:00 AM to discuss the remaining issues
- fax meeting minutes to the sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 25, 2000 **Time:** 3:30 – 4:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg Tablets

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance (statistics)

Meeting Chair: [redacted]

Meeting Recorder: [redacted]

External Lead: Nancy Buc

FDA Attendees:

[redacted] Office of Drug Evaluation III (ODEIII; HFD-103)
[redacted], Division of Reproductive and Urologic Drug Products (DRUDP ; HFD-580)
[redacted] Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
[redacted] Project Management Staff, DRUDP (HFD-580)

External Attendees:
Beverly Winikofi, M.D. – Population Council
Shelley Clark, Ph.D. – Population Council
Heather O'Neill – Danco Laboratories, LLC
Nancy Buc – Buc & Beardsley

Meeting Objective: The applicant requested this teleconference to clarify FDA-derived sample size calculations and to confirm the study endpoints for the referring versus non-referring physician study for post-approval (Phase 4 commitment) protocol.

Background: In teleconferences before August 23, 2000, FDA conveyed suggestions for study designs, endpoints and sample size estimates. The applicant's interpretation of the sample size calculations and endpoints are contained in their August 23 letter.

Discussion Items:

- Success rates of 92% and 95% were demonstrated in the clinical trials; rates of transfusions and hospitalizations were less than 1%
- the applicant is concerned the sample size of 120 per group is inadequate to yield a satisfactory upper limit of a confidence interval for the rate of a serious adverse event, such as transfusion, if the rate of a serious adverse event is approximately 1%

- endpoints of interest to be compared between the two groups need to include the success rate (e.g., approximately 92 or 95%) and its converse, the failure rate (i.e., 1- success rate); most failures, if not all, will likely result in surgical termination of pregnancy
- other endpoints of interest include rates of complication, (such as transfusions, hospitalizations, etc.)
- FDA would like to exclude an absolute difference of greater than 5% in efficacy between the two groups
- FDA also would like to exclude an absolute difference of greater than 5% in complication rates between the two groups
- FDA requests complication rates estimated separately for each group, but these estimates are not the ultimate goal of the Agency
- DRUDP agreed with the applicant's concern that 120 patients per arm is inadequate to yield an acceptable upper limit of a confidence interval for an estimated complication rate *within* a group; however, 120 patients is adequate for ruling out differences in rates of greater than 5% *between* groups.
- The FDA-derived estimate of 120 patients per arm was based on the following assumptions:
    - the endpoint is rate of complications
    - the referral and non-referral groups each have an underlying rate of 1%
    - the rates for the two groups do not differ by more than 5%
    - a 95% one-sided confidence interval for the differences in rates
    - approximately 80% power
    - a randomized study
    - no adjustments for dropouts
- DRUDP indicated a sample size of 629 per group is needed to insure with 80% power that the differences in success rates are within 5% of each other, assuming
    - a 95% two-sided confidence interval
    - underlying success rate per group is 92%
    - a randomized trial
    - no adjustments for dropouts
- for patients that are referred to a physician, the sponsor will need to obtain information through the referral facility
- the sponsor may be able to plan to have fewer sites in the non-referral arm; (e.g., if a historical control is used)
- if a historical control is used, the sponsor should demonstrate the similarities between the historical control population (and clinical trial procedures) to the current population (and to procedures in the current trial); any difference in population or procedures should be evaluated for their possible impact on the outcome of the trial; ideally, FDA would like a concurrent comparison between referring and non-referring physicians
- the sponsor would like to remove [redacted] because the [redacted] rate is so low
- the sponsor will maintain an audit of the physicians' compliance with the Medication Guide

APPEARS THIS WAY
ON ORIGINAL

Action Items:

- the sponsor should submit a proposal for the study described earlier including a sample size, referring physicians to get follow-up information on patients from referral facility (it built into the protocol); if the sponsor expects a lack of compliance, the sponsor can build this into the protocol
- the follow-up teleconference will be scheduled for Tuesday/Wednesday (meeting scheduled for Tuesday, August 29, 2000 @ 4:00PM if needed, for additional clarification (cancelled by sponsor)

/S/ — **Minutes Preparer**

/S/ 9/21/00 — **Concurrence, Chair**

- Note to Sponsor: These minutes are official minutes.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 9, 2000 **Time:** 2:00 – 2:30 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair: [redacted]

FDA Attendees:

[redacted] Office of Evaluation III (ODEII; HFD-103)
[redacted] Project Management Staff, DRUDP (HFD-580)

External Participant:
Nancy Buc

Meeting Objective: To discuss the status of pending issues pertaining to this drug product.

Discussion:

- the Population Council is in the process of writing a letter responding to the pharmacology, MedGuide, and the home-se issue
- the sponsor needs FDA clarification regarding Phase 4 study proposal comparing the results of the referring physicians versus the non-referring physicians to evaluate patients outcome
- the purpose of this study is to assure that the information gained from this study would be comparable to the clinical trial, it is necessary to measure the following items: medical abortion failure rate, Day 14 return rate, and complication rate (i.e., transfusion, hospitalization, surgery for bleeding, surgery for abortion, infection rate); with a low complication rate (1%), sponsor should calculate sample size based on change ≤5% for example (120 patients approximately) to give reassuring data; the sponsor and the Agency have not yet agreed on a percentage
- the sponsor is concerned that surgeons would do the surgical abortion quicker than a non-surgeon and would make the results of the study change
- the sponsor has planned intervention plans if the study results find problems between referral and non-referral physicians (education, seminars)
- the sponsor needs to build a protocol that would take into consideration the timing that a surgeon can perform a surgical abortion
- the sponsor needs to contact physicians that would be interested in participating in the study and make sure that all steps are followed to ensure patient/physician confidentiality
- the sponsor can collect intermediate data to locate any problems before completing the study
- the sponsor believes that there will be more complete data from the non-referral physicians because they will have patient information; this can be built into the protocol
- the sponsor will propose a protocol trying to address all issues that could occur during that study

- both the Agency and the sponsor agree that it is important for the patient to return to the physician on Day 14 to ensure the procedure is complete
- the sponsor will propose a plan to study the pregnancy outcomes of the referral versus the non-referral physicians; the sponsor agrees to supply information regarding the patients who remain pregnant after the medical abortion fails, but the sponsor would like to ensure patient confidentiality and will propose a way to keep patient information confidential
- the tradename review is not complete, but the Office finds the name is acceptable due to direct distribution
- the FDA is still discussing the need to audit the patient agreement for compliance; the sponsor would like to avoid any public uproar regarding privacy; the sponsor needs to propose a way to audit the patient agreement without having a public uproar regarding this matter
- the FDA would propose a Day 3 return with a 4 hour observation in order to return home; the sponsor does not agree with this but understands the FDA's position
- the sponsor needs to add information regarding the chance of malformation with the use of misoprostol; the sponsor does not agree because in their study they had no incidence of malformation
- the sponsor believes that having a Black Box Warning is not necessary [redacted] the Agency has added this information to the patient agreement because the Agency feels that there "may be a risk"; the Agency will review this information and comment further to the sponsor
- the sponsor is concerned with what would happen if the study results are not what they expected; the Agency would review the information accordingly and determine the cause of the differences, if any
- the Agency wants this information studied to ensure the safety of the patients versus numbers

Action Items:

- FDA will supply the sponsor with a draft MedGuide and Exhibit E comments
- The sponsor will submit draft labeling, Phase 4 proposals, and deficiency from inspection
- [redacted] will call Nancy Buc on 8-11-00 regarding the Black Box Warning

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: July 14, 2000 **Time:** 10:00 –11:30 AM **Location:** Parklawn; 13-45

NDA 20-687 **Drug:** mifepristone (200 mg) tablets

Indication: induction of abortion

Sponsor: Population Council

FDA Attendees:

[redacted] Office of Evaluation III (ODEIII; HFD-103)
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] Project Management Staff, DRUDP (HFD-580)

FDA Consultant:
Michael Green, M.D. - Reproductive Health Advisory Committee Chair (SGE consult) and Chair of the Pregnancy Labeling Subcommittee

Meeting Objective: Dr. Michael Green, Reproductive Health Advisory Committee Chair (SGE consult) and Chair of the Pregnancy Labeling Subcommittee, will be responding to the Agency questions regarding current thoughts and recommendations regarding this product provided with background materials.

Background: This application is in its third review cycle, and received an approvable action letter, February 18, 2000. In that approvable letter, the Agency outlined three areas that the sponsor needed to address: chemistry issues, the distribution system, and the labeling.

Discussion Points:

- in 1996 the Advisory Panel recommended distribution to physicians directly; the Agency is soliciting the advice of Dr. Green regarding this issue
- Dr. Green acknowledged that the data presented in the US study is very similar to that in the French; the US trial did seem to have a higher rate of surgical interventions to terminate pregnancies (8%) compared to the French study (5%), but he attributed this to American physicians initially not being familiar with the treatment and more comfortable with surgery. He stated overall the safety profile is good.
- Dr. Green concurred with the Agency in initially limiting the distribution of this drug directly to physicians only
- Dr. Green [redacted]
- Dr. Green discussed the qualifications needed to receive this drug product could include:
  - [redacted]
  - some states allow midwifes to practice independently and prescribe as physicians; there may need to be some language that would include these practitioners
  - the physician has to be able to detect an ectopic pregnancy
  - the physician has to be able to determine the gestational age
  - the physician must be able to have admitting privileges for emergency facilities

- the sponsor in previous submissions, planned to design a formal training program for the use of this drug product, but now does not feel this is necessary
- Dr. Green concurred with the sponsor's position because of the amount of literature there is regarding the safe use of this product that formal training or a certification training program is not needed at this time
- Dr. Green agreed with the Agency that the patient should be informed of the options and receive information regarding the drug product that they are about to receive; having the patient sign that they have received all the information and have read the material provided is adequate
- adverse events are not more likely if the patient returns home after the misoprostol is administered and Dr. Green was comfortable with home administration but stated that initially requiring return on Day 3 is not unreasonable until more experience is gained
- Dr. Green stated that the patient should be fully informed about the drug's risk and benefits and agree to some type of consent process to ensure that the woman is committed to termination and understands risks of drug (including teratogenic risk) and possible need for surgical termination. Dr. Green answered affirmative to FDA's question about should some physicians be audited to ensure the consent process is happening if the drug is approved.
- Dr. Green did not object to the drug having a Black Box warning. He stated the [redacted] should be in the Black Box. Dr. Green agrees with the Agency that the physician should have access to an emergency facility with no limitation on distance to that facility as was done in the clinical trial
- Dr. Green did not recommend that ultrasonography be mandated as a skill for practitioners to have to be distributed the drug, nor should it be mandatory for dating or confirming expulsion.
- Dr. Green stated that [redacted] should not be in the label
- Dr. Green considers this drug to be safe and effective and should be made available to the public, but it should not be overly burdensome to the provider

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: June 19, 2000 **Time:** 9:30 – 9:45 am **Location:** Parklawn, 17B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council/Danco

Type of Meeting: Guidance – CMC

FDA Meeting Chair: ———

External Chair: ———

FDA Attendees:

——— Division of New Drug Chemistry II, ONDC @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

——— Project Management Staff, DRUDP (HFD-580)

External Participant:

———

Meeting Objective: To discuss Danco's proposal to submit an upcoming CMC amendment to the pending NDA. (Attached facsimile was sent to ——— prior to this teleconference.)

Discussion:

- Danco indicated that several changes have been implemented at the factory including the validation process with ——— validation; these changes will be described and included in the upcoming amendment
- ——— facility inspection has been scheduled for July 24 – 28, 2000
- ——— will discuss the outstanding issues with the inspector prior to the inspection; one issue to verify is assurance that the process validation allows for the changes in the method; Danco confirmed that the ——— were run for validation in July and August 1999, prior to the last inspection in October 1999
- Over a total of — batches have been made to date
- ——— was conducted to verify ———

Decisions made:

- None

Action Items:

- Danco to submit CMC amendment by June 23, 2000

/S/

Minutes Preparer

/S/

Concurrence, Chair

Teleconference Minutes

Date: June 7, 2000 **Time:** 4:30 – 4:50 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Discussion of Press coverage

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER), FDA

[redacted] Project Management Staff, Division of Reproductive and Urologic Drug Products (HFD-580)

External Attendees:

[redacted]

Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To clarify FDA comments and recommendations from the June 1, 2000 teleconference, to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.

Discussion:

Restricted Distribution

- FDA clarified with Population Council, Danco and Ms. Buc that the sponsor understood that a public registry of physicians was not proposed by FDA; rather, the FDA has proposed qualifications for physicians to ensure that recipients of the drug product are adequately trained for the safe use of this drug product; the sponsor's proposal for a distribution system, submitted in response to the approvable letters, only provided for the physical handling of the drug product; thus, in keeping with the recommendations of the July 1996 Advisory Committee and in order to advance the review of this application FDA provided recommendations for sponsor's consideration; sponsor concurred that this was also their understanding of the FDA proposals
- today's Press coverage described a "public registry" implying that qualified physicians could be readily identified and the list of those physicians could be publicly available; Population Council and Danco stated that their public statements only described the FDA recommendations as "more restrictive than expected" and that they did not provide any information about a public registry

- FDA asked sponsor to consider addressing the misinformation in the Press regarding this product; sponsor stated they were willing to consider correcting these misstatements and would get back to FDA Thursday, June 8 or Friday, June 9, 2000

Communications with the FDA regarding review of application

- public communication of the negotiation processes related to this drug application review can hamper the collaborative efforts put forth thus far between FDA and sponsor; FDA has not provided any information regarding the review of this application to the public or Press
- open, confidential communication between the FDA and the sponsor is necessary to continue making progress on the review and approval of this application as there are many areas remaining on which to reach agreement; the sponsor agreed that these were their goals as well; labeling recommendations will be provided by mid-June; sponsor will respond to FDA recommendations for qualifications of physicians by June 23
- FDA proposed that sponsor request a face-to-face meeting to continue discussion in early July; sponsor will make this meeting request through ———

Decisions made:

- continue discussions of review issues in face-to-face in early July

Action Items:

- Population Council to inform FDA by June 9 of its intention to correct the misrepresentation regarding a public physician registry
- FDA to provide labeling revisions to sponsor in mid-June
- Population Council to provide responses to FDA proposed criteria for physician qualifications by June 23
- Population Council will request a meeting with ——— in early July and provide a package with a proposed agenda, questions and any relevant information for FDA consideration prior to this meeting
- FDA to provide copy of teleconference minutes to sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: June 1, 2000 **Time:** 1:00 – 1:30 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Advice

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation III

[redacted] Project Management Staff, Division of Reproductive and Urologic Drug Products

External Attendees:

[redacted]

Sandra Arnold, Population Council

Nancy Buc, Buc and Beardsley

Meeting Objective: To convey FDA comments and recommendations regarding the proposed restricted distribution, revised labeling and requested Phase 4 protocols for this application.

Discussion:

Phase 4 protocols

- the proposed protocols to address the Phase 4 commitments described in previous regulatory letters are to be submitted to FDA by August 1; sponsor expects to submit these protocols before August 1

Restricted Distribution

- a Subpart H requirement for this drug product continues to be under discussion in the Center; feedback may be available for sponsor regarding the FDA recommendation for Subpart H by the end of June 2000; a Subpart H requirement gives FDA authority to ensure compliance with restricted distribution
- if this product is approved not under Subpart H, a voluntary restricted distribution would still be necessary to assure adequate physical tracking and audit of the product and to assure that qualified physicians are certified to receive the product; sponsor's proposed distribution for physically tracking the product was proceeding in the right direction

APPEARS THIS WAY
ON ORIGINAL

- the following are additional FDA recommendations for criteria to assure the adequacy of qualifications for physician recipients (these criteria apply whether Subpart H is a condition for approval or whether there would be a voluntary restricted distribution system):

Proposed Restricted Distribution System for NDA 20-687

Qualifications for Physician Recipients:

1. Must be licensed to practice medicine in the state to which the drug is shipped.
   - acceptable documentation:
     - copy of valid physician's license

2. [redacted]
   - acceptable documentation:
     - sponsor to propose; self-attestation is discouraged

3. Has been trained to and has the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination.
   - acceptable documentation:
     - sponsor to propose; self attestation is discouraged

4. Has satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications.
   - acceptable documentation:
     - sponsor to propose curricula for review by FDA; sponsor to propose certification tracking system linked to the distribution system

5. Has continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or within one hour drive from the treatment facility.
   - acceptable documentation:
     - a signed letter by the Chief Medical Officer on the medical facility's stationary stating that the facility is properly equipped; sponsor to propose other acceptable documentation

Labeling recommendations

- revisions are being made to simplify the label and make it more effective for the clinician to use; revised labeling should be available to sponsor by mid-June
- FDA is proposing to delete the specific detailed references of the French data in the physician label to include only the most relevant data for clinician's to reference; inclusion of ranges that include the French data may be acceptable
- the Black Box Warning will remain in the label
- FDA recommends that the label should include the criteria that the patient [redacted] of an emergency medical facility to receive this product

- the WARNINGs section will include information about changes in bleeding and the need to confirm the loss of pregnancy in a followup visit
- FDA recommends deleting [redacted]
- FDA recommends that the misoprostol dose be given at a Second Visit in the clinic and that the patient must be observed for 4 hours post misoprostol as was studied in the clinical trials; once approved, the sponsor could supplement this NDA with the data to support changing this requirement for administering misoprostol in an in-office setting with 4 hours of post-dose monitoring
- FDA is recommending that the restricted distribution qualification requirements be listed in the HOW SUPPLIED section of the label for who would be eligible to receive the drug product
- although not a scheduled drug product, the label should emphasize the need to keep this product locked in a cabinet to assure the physical security and tracking of this product
- FDA will propose several revisions to the Patient Agreement Form; the patients will be required to initial each statement to assure an understanding and agreement of the information discussed; duplicate copies should be made so that the patient, medical record and distribution system are all assured to receive a separate copy of the Patient Agreement Form
- the labeling will refer to qualified recipients as physicians or doctors rather than "health care providers" to assure that only qualified physicians receive the drug product and assume the responsibilities under the distribution system; physician assistants and other health care professionals would not be qualified to receive this drug

Decisions made:

- further discussions between FDA and sponsor is needed before the action date for this application

Action Items:

- FDA to fax the list of Proposed Restricted Distribution System for NDA 20-687 (Qualifications for Physician Recipients) to sponsor (*NOTE: fax was sent by 2:00 pm June 1, 2000*)
- FDA to provide labeling revisions to sponsor in mid-June
- Population Council to provide responses to FDA proposed criteria for physician qualifications by mid-June
- Following reciept of FDA proposed labeling, Population Council will provide a request for a meeting and provide a package with proposed agenda, questions and any relevant information for FDA consideration prior to a meeting
- FDA to provide copy of teleconference minutes to sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: May 19, 2000 **Time:** 8:45-9:00 am **Location:** Parklawn; 18B-09

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Teleconference

Meeting Chair: [redacted]

External Lead: Sandra Arnold

Meeting Recorder: [redacted]

FDA Attendees:
[redacted] Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
[redacted] Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To discuss proposed distribution system with the sponsor and request that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product. To request Phase 4 Commitment summary protocols for review during this review cycle.

Discussion:
Distribution system:

We are actively reviewing the proposed labeling and the distribution system; final comments or decisions are pending, however, there are several issues to be addressed:

- The proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.
  - Patients must be assured that providers will be qualified physicians [redacted] Providers must be available to manage any emergency complications such as hemorrhage and incomplete abortions. [redacted]

- Appropriate provider qualifications must be specified in the distribution plan, and the sponsor will be required to audit the distribution system to assure that providers meet appropriate qualifications.

- Provide us with acceptable, auditable criteria, e.g., that they be licensed physicians. Other criteria may include Board certification (OB/GYN or FP?), certification of training &/or experience, hospital credentials/privileges, facility certification, documentation of number of procedures performed, etc.; designate how you will audit the designated criteria.

- Indicate how you will assess compliance by providers and include a provision to discontinue from the distribution plan any provider who does not comply with the requirements.

Phase 4 commitments

The requested Phase 4 commitments are not optional and are requirements for approval. Summary protocols for these commitments, need to be submitted by August 1 to allow for review prior to approval.

Action Items:

- Sponsor to provide proposal for appropriate provider qualifications to ensure safety and appropriate follow-up care for patients
- Sponsor to submit Phase 4 summary protocols for review by August 2000

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: April 26, 2000 **Time:** 11:44 – 12:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

FDA Attendees:

[redacted] Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

[redacted]

Meeting Objective: To communicate information to the sponsor regarding the methods validation package and clarification on the Phase 4 commitment in the February 18, 2000 approvable letter.

Decisions made:
Regarding Methods Validation Package

- the following information should be provided in the methods validation package:
  - the sponsor should prepare four sets of samples (two for the labs and two for back-ups)
    - include the reference standard for the drug substance from both Shanghai Hua Liau and Rousell
  - a list of the composition of the drug product
  - specifications for both the drug product and drug substance
  - a description of the methods with the method validation data
  - material safety data sheets

Regarding Phase 4 commitments

- the sponsor should submit a summary of the proposed protocols to the Division for review
- the summary protocols should include all the information outlined in the February 18, 2000 approvable letter and in the sponsor's letter dated September 16, 1996
- these summary protocols must be reviewed and approved by the Division prior to approval of this product

Action Items:

- fax meeting minutes to the sponsor within 30 days

/S/
Minutes Preparer

/S/ 4/26/00
Concurrence, Chair

Teleconference Minutes

Date: April 25, 2000 **Time:** 10:44 – 11:00 AM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

FDA Attendees:

[redacted], Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

[redacted]- Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

[redacted]

Meeting Objective: To communicate information to the sponsor regarding their response to three of the chemistry issues raised in the approvable letter.

Decisions made:

Drug Substance:

[redacted]

Drug Product:

[redacted]

Action Items:

- fax meeting minutes to the sponsor within 30 days

/S/

Minutes Prepared

/S/ 4/28/00

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

MAR 6 2000

Date: February 11, 2000 **Time:** 1:15 – 2:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** mifepristone 600 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation II (ODEII; HFD-102)
[redacted] Office of Drug Evaluation III (ODEIII; HFD-103)
[redacted] ODEIII (HFD-103)
[redacted] Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
[redacted] DNDCII @ DRUDP (HFD-580)
[redacted] Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-040)
[redacted] Project Management Staff, DRUDP (HFD-580)
[redacted] Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

[redacted]

Fred Schmidt – Population Council

[redacted]

[redacted]

Meeting Objective: To discuss the approaching goal date and the planned action for this application.

Decisions made:

- The Division will be issuing an approvable letter on February 18, 2000
- The approvable letter will outline the outstanding issues
  - Outstanding chemistry issues
  - Inspection of drug substance manufacturing site
  - Physician and Patient Labeling

- Conditions related to Subpart H approval, such as distribution of the drug, if and when this product is approved

- Mifeprex is not an acceptable tradename, but the tradename [redacted] was found to be acceptable by OPDRA
- If or when Danco issues a press release, they will provide a copy to DDMAC and DRUDP

Action Items:

- Fax meeting minutes to sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

MEMO OF TELEPHONE CONVERSATION

The sponsor was contacted on August 9, 1996, and the following questions were asked:

1) When will their proposed distribution system be submitted? ANS: Expect to send in next week.

2) Do you have an updated draft label? ANS: No waiting for comments from the FDA.

3) Do you have any more (new) post-marketing data from the regulatory agencies in countries in which this drug is approved for marketing (the Britain, Sweden and France)? ANS: No, we have no new data, but have yet to approach regulatory agencies. Please provide names and numbers of regulatory contacts if you have them. The sponsor was told that I would try and obtain this information for them but did not know if I would be successful.

The sponsor was also told that a letter requesting commitments to a variety of Phase IV studies would be sent within a week.

APPEARS THIS WAY
ON ORIGINAL

DATE August 9, 1996

NDA/IND NUMBER
NDA 20-687

INITIATED BY

HFD-580

PRODUCT NAME
Mifepristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Robbins, PH.D.

TELEPHONE
(212) 327-8748

FAX

cc:
Orig. NDA
HFD-580/

8/9/96

DIVISION HFD-580

I spoke with Maggie Carlson, Director, Population Council and Ann Robins, Regulatory Affairs, Population Council today regarding their plans to submit preliminary information re: the results of the US trial of mifepristone as both part of their IND ——— and as part of the safety update to the NDA (20-687).

It was discussed that the Pop Council is performing a 100% audit of the data and sites (just as they did for the French data) and that therefore, the information submitted at this time would not be the final study report.

We agreed that they could submit a preliminary report to the IND and/or NDA. They acknowledge that the audit plans are there own and not a specific FDA requirement.

After submission of a preliminary report, the sponsor anticipates a brief review of the US data in their presentation to the Advisory/ Committee.

APPEARS THIS WAY
ON ORIGINAL

DATE May 24, 1996

NDA 20-687

—

INITIATED BY

———

HFD-510

PRODUCT NAME

Mifepristone

SPONSOR'S NAME

Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Margaret Catley-Carlson
Director

TELEPHONE

(212) 339-0501

CC:
NDA 20-687
HFD-510

———

/S/ 5-30-96

DIVISION HFD-510

FEB 23 1996

I contacted Catherine Euvard today and stated that it was my understanding that Roussel was planning to respond to the list of questions FAXed to them earlier. She stated that Roussel and the Pop. Council would have to discuss this because Roussel did not want to do anymore work. I said that it was my understanding that several of the questions were questions that only Roussel could answer, but that I did not want to get into the middle of something that Roussel and the Pop. Council had to work out. I stated that the reason I had called was to give them the name of someone who would help them to decide what needed to be put into their EA section. I then gave her ——— name and phone number.

Dr. Euvard stated that she did not understand why they had to submit an EA when they were not going to ever supply drug to the U.S. I told her that everyone understood that Roussel would not be supplying drug, however an NDA had to be complete in order for it to be reviewed and because they were listed in the IND as the manufacturer, they would have to submit all of the pieces.

Dr. Euvard said that she was not the one that made decisions, and did not understand all of the nuances, but that she would give the name and number of ——— to Joe Scheeren, who was not expected in until Friday, and he would get in touch with ———

APPEARS THIS WAY
ON ORIGINAL

DATE Februayr 12, 1996

NDA/IND NUMBER
IND ———

INITIATED BY

———

HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME

The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Dr. Catherine Euvard

TELEPHONE

9-011-33-1-4991-4252
FAX 9-011-33-1-4991-3119

cc:
uterine acting
HFD-510/ ———

DIVISION HFD-510

[redacted] called to clarify the contact made with Dr. Euvard on February 12, 1996. I said that I had called to give Roussel the name and number of a contact that could help them determine what they would have to provide, and what they would not have to provide in their EA section. I then gave the name of [redacted] again. [redacted] said that he had hoped that they would not have to have an EA section. I told him it had been decided in a higher level meeting that they would, but that this woman would be helping them.

[redacted] said that they only have [redacted] left of the drug substance that went into the making of the drug. I told him that I had given that question to [redacted] and he had said that it would be alright if the drug substance came from a different lot. However, [redacted] wanted to remind them that if reference standards were used in the methods of manufacture, that we would require the standards as well. I stated that I believed that this was a routine request, and should not be a surprise. [redacted] agreed that this was a standard request and that he would work on it. He also stated that Roussel was planning to respond to all the questions on our list.

I told him that I had one more concern. I noted that Roussel very obviously wanted to work through the Population Council to answer questions, and not directly with the FDA, and said that I understood this. However I requested that they think about how they wanted to answer any other chemistry questions that might come up during review if the Population Council was to be blind to the CMC section. I pointed out that the review that the reviewing chemist had done had been cursory, and meant only to cover obvious deficiencies. [redacted] said that Roussel was going to have an internal meeting to discuss these things, and that he would bring up that point.

Discussion ended at that point.

DATE February 14, 1996

NDA/IND NUMBER
IND [redacted]

INITIATED BY
[redacted]

HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
[redacted]

TELEPHONE
9-011-33-1-4991-4252

FAX
9-011-33-1-4991-3119

cc:
Uterine Acting
HFD-510, [redacted]

DIVISION HFD-510

MEMO OF TELEPHONE CONVERSATION

FEB 23 1996

Following my telephone conversation with Dr. Suvard I called [redacted] to let her know that [redacted] would be calling probably either the end of this week or the following week. I outlined the CMC problem, and [redacted] decision to have [redacted] get involved. I requested that if [redacted] had not contacted her by the end of next week, that she give me a call.

[redacted] said that she was going on vacation soon, but would be in the office on Monday. She also stated that if she had not heard from anyone by the 20th of February she would call me.

DATE February 12, 1996

NDA/IND NUMBER

[redacted]

INITIATED BY

[redacted]

HFD-510

PRODUCT NAME

Mifipristone

SPONSOR'S NAME

The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

[redacted]

TELEPHONE

[redacted]

cc:
Uterine Acting
HFD-510/ [redacted]

[redacted]

DIVISION HFD-510

ROUTING AND TRANSMITTAL SLIP

Date 5/17/90

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1.		
2.		
3.		
4.		
5.		

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

REMARKS

- to 5/17

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
/S/	Phone No.

5041-102

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

* U.S. GPO: 1990 — 262-080

APPEARS THIS WAY
ON ORIGINAL

MIF 002153

Printed by [redacted]

Electronic Mail Message

Date: 29-Aug-2000 11:14am
From: [redacted]

Dept:
Tel No:

TO: [redacted]

CC: [redacted]
Subject: Re: HuaLian 483 Response

[redacted]

I ' ve received Shanghai Hua Lian's Final Response, Aug. 25, 2000. The responses on the three items under Observation 5 are adequate.

[redacted]
Drug Group/DEIO

> -----Original Message-----
> From: [redacted]
> Sent: Monday, August 28, 2000 2:20 PM
> To: [redacted]
> Subject: HuaLian 483 Response
>
> [redacted]
>
> Today, I received HuaLian's Response to our 483. I reviewed the responses
> for my 483 observations and all appears to be adequate. [redacted]
> [redacted]
> [redacted]
> [redacted]
>
> Please let me know if you need any additional information or input from
> me.
>
>
> [redacted]
> [redacted], Kansas City District Office, FDA
> Phone [redacted] Voice-mail [redacted]
> FAX [redacted] E-mail: [redacted]
>
>

APPEARS THIS WAY
ON ORIGINAL

The Danco Group

November 29, 1999

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 037 - Chemistry, Manufacturing and Controls (CMC) Section 1 for Drug Substance: Amendment

Dear ———

This Amendment #037 to the NDA is an amendment to the CMC for our Drug Substance Manufacturer. It includes revisions based upon observations made to Shanghai HuaLian Pharmaceutical Co., Ltd. immediately following their Pre-Approval Inspection (PAI) on October 28, as well as other related revisions which the company felt were also appropriate.

Replacement pages are provided which are cross-referenced to the original Drug Substance CMC filed on June 3 as Amendment #025. Each replacement page has the change(s) highlighted in bold and italics and for your reference, each change is listed by page number in a Revision Summary.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely.

/S/

President and
Chief Executive Officer

APPEARS THIS WAY
ON ORIGINAL

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61 Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45 Contact telephone number is ———

/dns
Enclosures

cc: [redacted]

Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

[redacted]

[redacted] – FDA

APPEARS THIS WAY
ON ORIGINAL

Dr. Susan C. Haskell
851 19th Street
Des Moines, Iowa 50314

19-34550

SUMMARY OF FINDINGS:

This was a FY 99 High Priority CDER User Fee NDA Pre-Approval, Study Oriented, Clinical Investigator Data Validation Inspection issued from Good Clinical Practice Branch I, HFD-46, Division of Scientific Investigations, and it was conducted per CP 7348.811.

This was the initial inspection of this firm, it was pre-announced and a discussion was held relating to potential Y2K problems.

The study audited, Protocol Number 166A,B, was sponsored by The Population Council Inc. and it was entitled "EVALUATION OF THE EFFICACY, SAFETY, AND ACCEPTABILITY OF MIFERPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS".

During this inspection, no significant deviations were noted and no FDA-483 was issued.

Post-inspection correspondence should be mailed to:

Dr. Susan C. Haskell
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

Upon arrival at the firm, credentials and a notice of inspection were presented to Dr. Susan C. Haskell, Principal Investigator. Dr. Haskell introduced me to ——— the Study Coordinator. They were both present for the entire inspection.

Dr. Haskell was the primary person responsible for the conduct of the study. In addition to her overall responsibilities, she gave physicals, dispensed all of the medication, signed the informed consents, reviewed and signed the case report forms, reviewed and signed the ultrasounds and signed and made notes in the medical files.

——— course was listed as a subinvestigator on the 1572 but he ended up not participating in the study.

——— was responsible for the forms, ultrasounds, and case report forms.

and [redacted] were counselors for this study. They explained the procedure and obtained informed consent.

[redacted] were nurses for this study. They did the ultrasounds and were with the patients during the four hour monitoring period.

[redacted] is a nurse practitioner and performed physical exams during this study.

A copy of the study personnel signature registry is attached as Exhibit 1 and CVs for the people listed above are attached as Exhibit 2.

A list of studies Dr. Haskell has been involved in can be found on page 1 of Exhibit 2.

The protocol that was actually used appeared to be the same as the one sent with the background material and it is being returned.

Copies of the 1572s for this study are attached as Exhibit 3.

Copies of the patient informed consents that were used during this study are attached as Exhibit 4. Informed consent was obtained from each patient in this study.

All raw data for this study was available and all records were legible and orderly. No significant deviations were noted when comparing the case report forms to the medical files.

Test article accountability records were sufficient to reconcile the amount of test article received, dispensed, and or returned.

There appeared to be adequate follow-up of adverse reactions and a review of the records did not reveal any indication of underreporting of adverse reactions.

The IRB that was used was [redacted] The Chairman of the IRB is [redacted] The IRB's address is:

[redacted]

Informed consent was obtained from the first patient enrolled in this study on 11/2/94. The IRB approved the study on 10/12/94 and was kept informed of the progress of the

study. A copy of the approval letter is attached as Exhibit 5, and a copy of the firm's final report to the IRB is attached as Exhibit 6. A copy of the IRB roster is attached as Exhibit 7.

The lab that was used was [redacted] Certification papers for the lab were available for review. The address for the lab is:

[redacted]

[redacted] was responsible for monitoring this study in addition to providing the IRB. The monitors were [redacted]

A copy of the [redacted] site visit log is attached as Exhibit 8.

According to the Dr. Haskell, all of the CRFs were compared to the original records by the monitors and she felt the study protocol and record keeping requirements were adequately explained.

When I completed my audit, I met with Dr. Haskell and [redacted] I told them I had found no significant deviations from the regulations; however, I explained that the Center reserved the right to give the final classification of the inspection and they might have some comments on the material collected during the inspection. I then thanked them for their cooperation and concluded the inspection.

EXHIBITS:

1. Study Personnel Signature Register
2. CVs
3. 1572s
4. Informed Consents
5. IRB Approval Letter
6. Final Report
7. IRB Roster
8. [redacted] Site Visit Log

/S/

Investigator, KAN-DO

DEPARTMENT OF HEALTH AND HUMAN SERVICES

1934550

Food and Drug Administration
Kansas City District
Southwest Region
P.O. Box 15905
Lenexa, Kansas 66285-5905

Telephone: ———

February 16, 2000

Susan C. Haskell
Principal Investigator
Dr. Susan C. Haskell
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, IA 50314

Dear Madam:

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at Des Moines, IA on 11/18/99 by the U.S. Food and Drug Administration (FDA). When the agency concludes that an inspection is "closed" under 21 CFR 20.64(d)(3), it will release a copy of the EIR to the inspected establishment. This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to April 1, 1997, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The Agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it reflects redactions made by the Agency in accordance with the FOIA and Title 21, Code of Federal Regulations, Part 20. This, however, does not preclude you from requesting, and possibly obtaining any additional information under FOIA.

If there is any question about the released information, please feel free to contact ———, at ——— or write to her at the address listed on the letterhead above.

Sincerely,

/S/ ———

———

Kansas City District

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

CEN

Food and Drug Administration
Rockville MD 20857

JAN 18 1999

Susan Haskell, M.D.
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

Dear Dr. Haskell:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 166A) of mifepristone that you conducted for Population Council.

Between November 16 and November 18, 1999, [redacted], representing the Food and Drug Administration (Agency), inspected the study identified above. From our evaluation of the inspection report prepared by [redacted] and copies of study records obtained during the inspection, we conclude that you conducted your study in compliance with the Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of the Agency's Bioresearch Monitoring Program This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator [redacted] during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

[redacted]

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite [redacted]
Rockville, MD 20855

PROFESSIONAL HISTORY

PHYSICIAN - Iowa License
Nebraska License

- PLANNED PARENTHOOD OF GREATER IOWA, Des Moines, Iowa
  - -- Medical Director - 1991 to present
  - -- Physician Director of Surgical Services - 1991 to present
  - -- First and early mid-trimester abortions - 1990 to present

- PRIMARY INVESTIGATOR
  - -- Population Council Study: "Refining The Yuzpe Method of Emergency Contraception" - 1997 to present
  - -- Pharmacia-Upjohn Research Project: "A Comparative Study of the Efficacy, Safety, and Patient Acceptability of CYCLO-PROVERA™ Sterile Aqueous Suspension and ORTHO-NOVUM® 7/7/7, 28 Tablets" - 1997 - present
  - -- Planned Parenthood Federation of America study: "A Project to Study the Safety and Efficacy of Methotrexate and Misoprostol for Early Induced Abortions" 1996 - present
  - -- Population Council Study: "Evaluation of the Efficacy, Safety, and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days" -- 1994 to 1995

- GUEST LECTURER
  - -- Starting Medical Abortion Services; PPFA conference, 1996
  - -- Options for Early Abortion; Planned Parenthood of East Central Illinois, 1996
  - -- Clinic Trials of M & M-Contraceptive Update; St. Paul, Minnesota, 1995
  - -- Abortion; University of Northern Iowa, 1993-1994

- PARTNER AND PHYSICIAN - Altoona Family Practice Center, PC, Altoona, Iowa -- 1982 to 1991

- PHYSICIAN - Iowa Correctional Institution for Women, Mitchellville, Iowa
  - -- 1982 to 1983

EDUCATION

Medicine

- American Osteopathic Board of Family Physicians - Board Certification in Family Practice, 1988
- Rotating Internship - Des Moines General Hospital, 1981
- University of Osteopathic Medicine and Surgery, Des Moines, IA - Doctor of Osteopathy, 1980
- Drake University, Des Moines, IA - Pre-med courses, 1974-1977
-
-

MEMBERSHIPS

- National Abortion Federation
- Association of Reproductive Health Professionals
- American Osteopathic Association
- American College of Osteopathic Family Physicians

11/16=18/99
EFR Dr. Susan C. Haskell CFN
Des Moines, Iowa 50314
Exhibit 2 Page 1 of 17

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)

1. NAME AND ADDRESS OF INVESTIGATOR

Dr. Sue Haskell, D.O.
851 19th Street
Des Moines, Iowa 50314

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

on site lab for preg tests, Hct, and Rh typing

[ ] for tissue examination

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

[ ]

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

EIR — 11/16=18/99
Dr. Susan C. Haskell CFN 19-34550
Des Moines, Iowa 50314
Exhibit 3 Page 1 of 3

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol [redacted] to 63 Days

Protocol #166A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)
(See instructions on reverse side.)

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Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

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on site lab for preg tests, Hct, and Rh typing

[redacted] for tissue examination

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

[redacted]

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

[redacted]

EIR 11/16=18/99
Dr. Susan C. Haskell CFN 19-34550
Des Moines, Iowa 50314
Exhibit 3 Page 2 of 3

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

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 #160A

TTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☒ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

)MMITMENTS:

agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

agree to personally conduct or supervise the described investigation(s).

agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

mplete all sections. Attach a separate page if additional space is needed.

tach curriculum vitae or other statement of qualifications as

tach protocol outline as described in Section 8.

gn and date below.

11/16=18/99
EIR
Dr. Susan C. Haskell CFN 19-34550
Des Moines, Iowa 50314
Exhibit 3 Page 3 of 3

ORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).
NVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

IGNATURE OF INVESTIGATOR	11. DATE
Sue Haskell DO	9-16-94
Sue Haskell DO	9 16 - 94

ic reporting burden for this collection of information is estimated to average 84 hours per response, including ime for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, completing reviewing the collection of information. Send comments regarding this burden estimate or any r aspect of this collection of information, including suggestions for reducing this burden to:

orts Clearance Officer, PHS
ert H. Humphrey Building, Room 721-B
ndependence Avenue, S.W
ington, DC 20201
: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0014
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

APPROVED BY
IRB

October 13, 1994

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 NUMBER: 166 A

1. Purpose and aims of the study

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 per cent of women. Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Approximately 250,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved for routine use in France for women who have been pregnant for seven weeks or less. Mifepristone in combination with a prostaglandin has also been approved for use in China, Britain and Sweden. In the latter two countries, it is used in women who are pregnant for nine weeks or less.

The aims of the present study are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who are 63 days or less from the first day of the last menstrual period. Three groups of women who are less than 50 days; 50 through 56 days and 57 through 63 days from the first day of the last menstrual period will be included in the study. This study is being performed as a requirement for registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for pregnancy termination in the U.S.

2. Clinic visits

I understand that at my initial visit (visit 1) I will receive counseling about the method, and a urine and blood sample will be collected to make sure I am pregnant. I will be given a physical, and a pelvic exam and my medical history will be taken. Using a vaginal ultrasound, which is a small probe that is placed in the vagina, the duration of my pregnancy will be determined. Also I will be given a blood test for the Rh factor in my blood. If I have an Rh negative blood type, I will be given an injection at the second visit to prevent the development of antibodies that could endanger any future pregnancy. In order to terminate my pregnancy, I will take three tablets of mifepristone (first medication) orally in the presence of study personnel.

October 13, 1994

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 NUMBER: 166 A

Two days later, I will return to the clinic (visit 2) even if I believe I have aborted and will take two misoprostol tablets (second medication) by mouth if I have not aborted. If I take the second medication, the duration of my stay at the clinic at the second visit will be approximately four hours, during which time I will be closely monitored by the study team. During this time, there is an 60-80% chance that abortion will occur. If I come to the clinic in a car, I will be sure to arrange for someone else to drive me home from this visit, and understand that I will not drive myself home. I understand that if the abortion does not occur at the clinic, it is likely to occur at home and I may continue to have uterine bleeding similar to a heavy menstrual period for several days. I should use sanitary napkins until the uterine bleeding or spotting ends and not use tampons. As with surgical abortion, I cannot resume douching until the bleeding stops (about 10-12 days). I should not resume sexual intercourse for eight to ten days after taking the prostaglandin, by which time most abortions would have been completed.

I understand that I may see the product of conception on my sanitary napkin or in the toilet. This may happen at the clinic, at home or work. Through the seventh week after conception, this product is called an embryo; it is smaller than a quarter and is usually embedded in a blood clot. Even if I see the products of conception, I will not be able to tell whether the method has been effective as part of the placenta may still remain in the uterus. This is why it is important to return to the clinic for a follow-up, visit 3, so that the clinic staff can determine if the abortion is complete.

A further appointment will be made for me to return to the clinic two weeks after taking the first tablet (visit 3), to ensure that the treatment has been effective. If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be carried out at that time to complete the abortion. This is the same surgical procedure that would have been used had I elected to undergo surgical abortion in the first instance. I will be sure to have arranged for someone else to drive me home from this visit, and understand that I will not drive myself home. If I notice a vaginal discharge with odor after treatment, this may indicate an infection. I will contact my physician for an appointment.

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

APPROVED BY
IRB
OCT 27 1994

October 13, 1994

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 NUMBER: 166 A

I understand that there are no indications at present that use of an antiprogestin to end a pregnancy has prevented or harmed a woman's ability to have a baby in the future. Women who have taken mifepristone have been able to conceive and subsequently bear a healthy child. Since it is possible to become pregnant again after the abortion, I will be asked to select and use a contraceptive method.

3. Benefits

I understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. There is no anesthesia-related risks or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study that may make mifepristone/misoprostol available to women in the U.S.

4. Risks and discomforts

I understand that drawing blood for the tests at the first visit may be associated with discomfort, bruising, and possibly infection at the site of withdrawal. I understand that experience gained so far with the combination of drugs and the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications are comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or cramps which are similar to those associated with a very heavy menstrual period. I will receive appropriate medication for pain when required. I understand that I should not take aspirin, Motrin®, ibuprofen (Advil®) or any other drug known to block the action of prostaglandins. However, I may take Tylenol® and I may receive stronger medications for pain from my doctor. I understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. Uterine bleeding, similar to a heavy period and lasting at least one week, may be expected. In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion.

APPROVED BY
IRB
OCT 27 199[illegible]

October 13, 1994

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 NUMBER: 166 A

I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. I understand that abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women. When abortion is incomplete, vacuum aspiration or dilatation and curettage are recommended to terminate bleeding and prevent anemia. *When abortion does not occur, surgical termination of pregnancy is recommended because of the possible risk to the fetus. I have previously agreed to this procedure.*

There have been no serious heart conditions in the 52,000 women using the combination of drugs in the study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare (one in 20,000 cases). To date there is no evidence that the oral prostaglandin (misoprostol) that I will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

5. Alternative Statement

I know that my pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to me. The advantages of surgical termination of pregnancy is that this is a one day procedure. The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

APPROVED BY

IRB

October 13, 1994

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 NUMBER: 166 A

6. Physical Injury Statement

If I require medical treatment as a result of physical injury arising from my participation in this study, immediate, essential, short-term medical care and treatment as determined by the doctors in this study will be made available without charge to me. There will be no monetary compensation for any other care, but medical consultation and appropriate referral services are available. Further information on the availability of medical care and treatment for any physical injury resulting from my participation in this study may be obtained from the Investigator, Dr. Susan Haskell (telephone: (515) 280-7000) or (1-800) 568-2404.

7. Whom to Call in an Emergency

I understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, I will report immediately to Planned Parenthood of Greater Iowa, 851 19th Street, Des Moines, IA 50314. In addition, I will contact Dr. Haskell (telephone:(515) 280-7000). If he or she cannot be reached in a medical emergency related to the study, I may contact ———— at (515) 280-7000 or (1-800) 568-2404.

8. Offer to Answer Questions and Freedom to Withdraw from the Study

I have been told that I may withdraw from the study at any time without jeopardy to my present or future medical care from the hospital or clinic. If I withdraw I will be offered a surgical abortion. I have been told to contact Dr. Haskell Telephone: (515) 280-7000 or ———— Telephone: (515) 280-7000 if I have any questions about the research. These physicians may appoint their associates to answer my questions.

I also understand that the Principal Investigator may require me to withdraw from the study, if in his/her medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

I understand that, if my treatment under the study does not result in an abortion, and if I refuse surgical abortion and continue with my pregnancy, I risk and the infant may risk, complications, including fetal or infant malformation.

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IRB

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 NUMBER: 166 A

9. Confidentiality

I understand that information obtained in this study will be transmitted only in a form that cannot be identified with me, and that all records will be kept in a locked cabinet. I understand that the Population Council or their designated monitors, as well as the U.S. Food and Drug Administration may request access to my medical records.

10. Subject's Statement

I, the undersigned, have had the risks and benefits of this study explained to me in a language that I understand. I agree to participate in this study as a volunteer subject.

_____ Date

_____ Signature of Volunteer

11. Investigator's Statement

I, the undersigned, have explained to the volunteer in the language which she speaks the procedures to be followed in this study and the risks and benefits involved.

_____ Date

_____ Signature of Investigator

_____ Date

_____ Signature of Witness to the Above Signatures and Explanation

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OCT 27 1994

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DATE ASSGND: 9/99 PRIORITY: 1 DATE INSPD: 11/16-18/99 GRP:
CENTRAL FILE NO.: 19-34550 JD/TA: CNTY: PHONE: (515) 280-7000
EMPL NO:
NAME: Dr Susan C. Haskell
CITY: Des Moines STATE: IA ZIP: 50314 STREET: 851 19th Street DISTRICT: C

ENDORSEMENT

This was a FY99 High Priority CDER User Fee NDA Pre-Approval, Study Oriented, Clinical Investigator Data Validation Inspection issued from Good Clinical Practice Branch 1, HFD-46, Division of Scientific Investigations, And it was conducted per CP 7348.811.

This was the initial inspection of this firm, it was pre-announced, and a discussion was held relating to potential Y2K problems.

The study audited, Protocol Number 166A, B, was sponsored by the Population Council Inc. And it was 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".

During this inspection, no significant deviations were noted and no FDA-483 was issued.

[redacted] No follow-up is planned unless requested by the Center.

COMPLIANCE ACHIEVEMENT DATA

PAC	PROBLEM TYPE	CORR ACTION	EST COST ACTION	DATE ACTION VERIFIED	CORR UNIT	REPT DIST	REASON FOR CORRECTION

P HOME DIST /_____/ EMP NUM _____

SIGNATURE /S/ DATE: 11/24/99

DISTRIBUTION: CC: KANDO (Then —) (S) 11/23/99
CC: HFD-46 (ALL)
CC: Des Moines RP (C/S + EIR)
CC: BIMO Team (C/S only)
CC: — (C/S, 482)

[redacted]

MIF 002172

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 NUMBER: 166 A

1. Purpose and aims of the study

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. **Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone. In women whose first day of their last menstrual period occurred from 50 to 63 days before they received mifepristone, this new information suggests that as many as one in four may require some form of surgical procedure. There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea**** [1] Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Over 150,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved for routine use in France for women who have been pregnant for seven weeks or less. Mifepristone in combination with a prostaglandin has also been approved for use in China, Britain and Sweden. In the latter two countries, it is used in women who are pregnant for nine weeks or less.

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[1] Amendment 3 dated May 2, 1995

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 NUMBER: 166 A

The aims of the present study are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who are 63 days or less from the first day of the last menstrual period. Three groups of women who are less than 50 days; 50 through 56 days and 57 through 63 days from the first day of the last menstrual period will be included in the study. This study is being performed as a requirement for registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for pregnancy termination in the U.S.

2. Clinic visits

I understand that at my initial visit (visit 1) I will receive counseling about the method, and a urine and blood sample will be collected to make sure I am pregnant. I will be given a physical, and a pelvic exam and my medical history will be taken. Using a vaginal ultrasound, which is a small probe that is placed in the vagina, the duration of my pregnancy will be determined. Also I will be given a blood test for the Rh factor in my blood. If I have an Rh negative blood type, I will be given an injection at the second visit to prevent the development of antibodies that could endanger any future pregnancy. **I understand that I may be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, as well as determine the normal characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study*** [2]. In order to terminate my pregnancy, I will take three tablets of mifepristone (first medication) orally in the presence of study personnel. Two days later, I will return to the clinic (visit 2) even if I believe I have aborted and will take two misoprostol tablets (second medication) by mouth if I have not aborted. If I take the second medication, the duration of my stay at the clinic at the second visit will be approximately four hours, during which time I will be closely monitored by the study team. During this time, there is an 60-80% chance that abortion will occur. If I come to the clinic in a car, I will be sure to arrange for someone else to drive me home from this visit, and understand that I will not drive myself home.

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[2]Amendment 2 dated April 27, 1995

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 NUMBER: 166 A

I understand that if the abortion does not occur at the clinic, it is likely to occur at home and I may continue to have uterine bleeding for several days. **I understand that the amount of bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period**[3]. I should use sanitary napkins until the uterine bleeding or spotting ends and not use tampons. As with surgical abortion, I cannot resume douching until the bleeding stops (about 10-12 days). I should not resume sexual intercourse for eight to ten days after taking the prostaglandin, by which time most abortions would have been completed.

I understand that I may see the product of conception on my sanitary napkin or in the toilet. This may happen at the clinic, at home or work. Through the seventh week after conception, this product is called an embryo; it is smaller than a quarter and is usually embedded in a blood clot. Even if I see the products of conception, I will not be able to tell whether the method has been effective as part of the placenta may still remain in the uterus. This is why it is important to return to the clinic for a follow-up, visit 3, so that the clinic staff can determine if the abortion is complete.

A further appointment will be made for me to return to the clinic two weeks after taking the first tablet (visit 3), to ensure that the treatment has been effective. **I understand that I may again be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, and to determine the characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.*** [4] If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be carried out at that time to complete the abortion. This is the same

[3] Amendment 3 dated May 2, 1995

[4] Amendment 2 dated April 27, 1995

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

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surgical procedure that would have been used had I elected to undergo surgical abortion in the first instance. I will be sure to have arranged for someone else to drive me home from this visit, and understand that I will not drive myself home. If I notice a vaginal discharge with odor after treatment, this may indicate an infection. I will contact my physician for an appointment.

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

I understand that there are no indications at present that use of an antiprogestin to end a pregnancy has prevented or harmed a woman's ability to have a baby in the future. Women who have taken mifepristone have been able to conceive and subsequently bear a healthy child. Since it is possible to become pregnant again after the abortion, I will be asked to select and use a contraceptive method.

3. Benefits

I understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. There is no anesthesia-related risks or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study that will make mifepristone/misoprostol available to women in the U.S.

4. Risks and discomforts

I understand that drawing blood for the tests at the first **and third visits** may be associated with discomfort, bruising, and possibly infection at the site of withdrawal. I understand that experience gained so far with the combination of drugs and the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications are comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

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cramps which are similar to those associated with a very heavy menstrual period. I will receive appropriate medication for pain when required.

I understand that I should not take aspirin, Motrin®, ibuprofen (Advil®) or any other drug known to block the action of prostaglandins. However, I may take Tylenol® and I may receive stronger medications for pain from my doctor. I understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. I **understand that uterine bleeding, similar to that which occurs during a spontaneous miscarriage (i.e. more than a** heavy menstrual period) and lasting at least one week, may be expected. **The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period**[5]** In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion.

I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. I understand that based on prior studies and recently obtained information, abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone. In women whose first day of their last menstrual period occurred from 50 to 63 days before they received mifepristone, this new information suggests that as many as one in four may require some form of surgical procedure.**

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[5] Amendment 3 dated May 2, 1995

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When abortion is incomplete, vacuum aspiration or dilatation and curettage are recommended to terminate bleeding and prevent anemia. *When abortion does not occur, surgical termination of pregnancy is recommended because of the possible risk to the fetus. I have previously agreed to this procedure.*

There have been no serious heart conditions in the 52,000 women using the combination of drugs in the study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare (one in 20,000 cases). To date there is no evidence that the oral prostaglandin (misoprostol) that I will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

5. Alternative Statement

I know that my pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to me.

The advantages of surgical termination of pregnancy is that this is a one day procedure.

The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

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6. Physical Injury Statement

If I require medical treatment as a result of physical injury arising from my participation in this study, immediate, essential, short-term medical care and treatment as determined by the doctors in this study will be made available without charge to me. There will be no monetary compensation for any other care, but medical consultation and appropriate referral services are available. Further information on the availability of medical care and treatment for any physical injury resulting from my participation in this study may be obtained from the Investigator, Dr. Sue Haskell at 515-280-7000 or 1-800-568-2404.

7. Whom to Call in an Emergency

I understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, I will report immediately to Planned Parenthood of Greater Iowa, 851 19th Street, Des Moines, Iowa 50314. In addition, I will contact Dr. Haskell at 515-280-7000. If he or she cannot be reached in a medical emergency related to the study, I may contact ———— at 515-280-7000 or 1-800-568-2404.

8. Offer to Answer Questions and Freedom to Withdraw from the Study

I have been told that I may withdraw from the study at any time without jeopardy to my present or future medical care from the hospital or clinic. If I withdraw I will be offered a surgical abortion. I have been told to contact Dr. Haskell or ———— at 515-280-7000 if I have any questions about the research. These physicians may appoint their associates to answer my questions.

I also understand that the Principal Investigator may require me to withdraw from the study, if in his/her medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

I understand that, if my tre+atment under the study does not result in an abortion, and I refuse surgical abortion and continue with my pregnancy, I risk, and the infant may risk, complications, including fetal or infant malformation.

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PROTOCOL NUMBER: 166 A

9. Confidentiality

I understand that information obtained in this study will be transmitted only in a form hat cannot be identified with me, and that all records will be kept in a locked cabinet. understand that the Population Council or their designated monitors, as well as the U.S. Food and Drug Administration may request access to my medical records.

I understand that I may be asked to be interviewed by a representative of the ponsor. The interview will be conducted in the language that I speak and will verify hat I understand the risks, benefits, procedures, and the experimental nature of the tudy. If I do not agree to be interviewed, this will not affect my present or future edical care from the hospital or the clinic, or my participation in the study. I nderstand that I can change my mind at any time. All information will be kept onfidential.

10. Subject's Statement

I, the undersigned, have had the risks and benefits of this study explained to me in a language that I understand. I agree to participate in this study as a volunteer subject.

Date	Signature of Volunteer

11. Investigator's Statement

I, the undersigned, have explained to the volunteer in the language which she speaks the procedures to be followed in this study and the risks and benefits involved.

Date	Signature of Investigator
Date	Signature of Witness to the Above Signatures and Explanation

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EVALUACIÓN DE LA EFICACIA, SEGURIDAD Y ACEPTABILIDAD DE LA MIFEPRISTONA Y EL MISOPROSTOL PARA INDUCIR EL ABORTO EN LA MUJERES EN ESTADO DE EMBARAZO CON AMENORREA HASTA 63 DÍAS DE DURACIÓN

PROTOCOLO NUMERO 166 A

1. Propósito y objetivo del estudio

Es posible inducir el aborto en las mujeres que están embarazadas sin desearlo si toman mifepristona en combinación con una prostaglandina (misoprostol). La mifepristona es una droga que bloquea la acción de la progesterona, una hormona necesaria para mantener el embarazo. Una de las acciones de la mifepristona es la de interrumpir el embarazo en sus primeras etapas. Las prostaglandinas son substancias naturales creadas por el recubrimiento interior de la matriz durante la menstruación y que causan la contracción de la matriz. Durante las primeras etapas del embarazo, la mifepristona con misoprostol causan el aborto en, aproximadamente, el 95 por ciento de las mujeres. Las ventaja principal de este método de terminar el embarazo es que no se introducen instrumentos quirúrgicos en la matriz. Alrededor de 250,000 mujeres en 20 países han usado la mifepristona y una prostaglandina como un método médico para interrumpir el embarazo. La mifepristona y el misoprostol han sido utilizados por más de 50,000 mujeres en la dosis que se utilizará en este estudio. La dosificación que se va a estudiar ha sido aprobada en Francia para su uso de rutina por mujeres que tienen seis semanas o menos de embarazo. La mifepristona combinada con una prostaglandina también ha recibido aprobación para el uso en China, Gran Bretaña y Suecia. En los últimos dos países, la utilizan mujeres que tienen nueve semanas o menos de embarazo.

El objetivo del presente estudio es determinar la seguridad, eficacia y aceptabilidad de la mifepristona con misoprostol para terminar el embarazo en mujeres que hayan tenido el primer día de su último período mensual hace 63 días o menos. Tres grupos de mujeres con menos de 50 días; de 50 a 56 días y de 57 a 63 días desde el primer día del último período mensual se incluirán en el estudio. Este estudio se está llevando a cabo como un requisito para la registración de la mifepristona con misoprostol en la Administración de Alimentos y Medicinas de los Estados Unidos (Food and Drug Administration - FDA) para que estos productos se puedan usar para terminar embarazos en los Estados Unidos.

2. Visitas a la clínica

Tengo entendido que en mi primera visita (visita 1) seré asesorada sobre este método y se obtendrá una muestra de mi orina y sangre para asegurarse que estoy embarazada. Se me hará un examen médico, se examinará mi pelvis y tomarán mi historia clínica. Se determinará la duración de mi embarazo utilizando un ultrasonido vaginal, que es una sonda pequeña que se coloca dentro de la vagina. También, se me hará un análisis de sangre para ver si tengo el factor Rh en mi sangre. Si tengo el tipo de sangre Rh negativo, me pondrán una inyección durante la segunda visita para evitar que se desarrollen anticuerpos que pudiesen poner en peligro cualquier embarazo futuro. Para poder terminar mi embarazo, tomaré por vía oral tres tabletas de mifepristona (el primer medicamento) en presencia del personal del estudio.

Dos días después regresaré a la clínica (visita 2) aunque yo piense que he abortado y me tomaré por vía oral dos tabletas de misoprostol (segundo medicamento) si no he abortado. Si me tomo el segundo medicamento, la duración de mi estancia en la clínica durante la segunda visita será de aproximadamente cuatro horas. Durante ese tiempo seré cuidadosamente vigilada por el equipo del estudio. Durante este tiempo hay una oportunidad de un 60%-80% de que ocurra el aborto. Si vengo a la clínica en carro, me aseguraré de tener a alguien que me regrese a la casa después de esta visita. Entiendo que yo no puedo ir guiando hasta mi casa. Entiendo que si el aborto no ocurre en la clínica, ese muy probable que ocurra en la casa y puede que siga sangrando por el útero durante varios dias, parecido a una regla mensual fuerte. Debo usas almohadillas sanitarias hasta que deje de sangrar del útero o que las manchas terminen y no debo usar tampones. Al igual que con un aborto quirúrgico, no puedo volver a hacerme lavados vaginales ("douching") hasta que deje de sangrar (de 10-12 días). No debo volver a tener relaciones sexuales hasta después de ocho a diez días de haber tomado la prostaglandina, pues después de ese tiempo la mayoría de los abortos han terminado.

Yo entiendo que es posible que vea el producto de la concepción en la almohadilla sanitaria o en el excusado. Esto puede suceder en la clínica, en la casa o en el trabajo. Hasta la séptima semana después de la concepción este producto se llama un embrión; es más pequeño que una moneda de veinticinco centavos y generalmente está incrustado dentro de un coágulo de sangre. Aunque yo vea el producto de la concepción, no podré darme cuenta si el método ha tenido éxito ya que puede quedarse parte de la placenta en el útero. Por esto es importante regresar a la clínica para el seguimiento, la visita 3, para que los empleados de la clínica puedan determinar si el aborto ha sido completo.

Se me dará una cita para que regrese a la clínica dos semanas después de haber tomado la primera tableta (visita 3) para estar seguros que el tratamiento ha tenido efectividad. Si el tratamiento no ha tenido efectividad, entonces en ese momento se llevará a cabo un procedimiento quirúrgico llamado aspiración al vacío o dilatación y curetaje para terminar el aborto. Este es el mismo procedimiento quirúrgico que hubiese recibido si hubiese decidido hacerme un aborto quirúrgico desde el principio. Estaré segura de tener a alguien que me lleve para la casa en carro después de esta visita y entiendo que yo misma no puedo manejar. Si me doy cuenta que después del tratamiento tengo un flujo vaginal que tiene olor, puede indicar una infección. Me pondré en contacto con mi médico para hacer una cita.

Entiendo que la sangre puede continuar después de mi tercera visita. Si esto sucede, la clínica se pondrá en contacto telefónico conmigo para determinar si ya ha parado o si necesito tratamiento adicional.

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Yo entiendo que hasta ahora no ha habido indicaciones que el uso una antiprogestina para terminar un embarazo no ha evitado ni ha dañado la capacidad de una mujer de tener un bebé en el futuro. La mujeres que han tomado mifepristona han podido concebir después y han tenido hijos saludables. Ya que es posible volver a quedar embarazada después del aborto, se me pedirá que seleccione un método para evitar los hijos.

3. Beneficios

Entiendo que la ventaja del método para terminar un embarazo utilizando mifepristona/misoprostol es que evita un procedimiento quirúrgico. No hay riesgos relacionados con la anestesia no riesgo de perforación del útero o de lesiones al conducto cervical que ocurre raras veces después de terminar un embarazo de forma quirúrgica. Otro beneficio es la satisfacción de participar en el estudio que hará que las mujeres de los Estado Unidos tengan disponibles la mifepristona/misoprostol.

4. Riesgos y molestias

Entiendo que cuando me saquen la sangre para los análisis en la primera visita puedo sentir molestia, tener moretones y puede ocurrir una infección en el sitio de donde se sacó la sangre. Entiendo que la experiencia que existe hasta ahora con la combinación de drogas y el terminar un embarazo de poco tiempo indica que esta terapia tiene pocas reacciones secundarias. La frecuencia de complicaciones de corta duracion se puede comparar con la que se observa después de un aborto quirúrgico hecho con aspiración al vacío. La queja más común durante el tratamiento (en particular después de la administración del segundo medicamento) es dolor en el bajo vientre o retorcijones parecidos a los que se relacionan con un período mensual fuerte. Recibiré el medicamento apropiado contra el dolor cuando sea necesario. Entiendo que no debo tomar aspirina, Motrin®, ibuprofen (Advil®) o cualquier otra droga que se sabe bloque la acción de las prostaglandinas. Sin embargo, puedo tomar Tylenol® y mi médico me puedo recetar medicamentos más fuertes contra el dolor. Entiendo que los retorcijones y los dolores abdominales es una parte del proceso del aborto normal y esperada. Se ha observado la existencia de nauseas, vómitos y diarrea después de la administración del segundo medicamento. Por lo tanto, es necesario quedarse en la clínica bajo la supervisión apropiada en la segunda visita durante alrededor de cuatro horas antes de regresar a la casa. Se puede esperar sangre del útero, parecida a una menstruación fuerte y de una semana de duración. En raras ocasiones, puede haber mucha sangre del útero que cause la necesidad de hacer un aborto quirúrgico y/o una transfusión de sangre.

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Entiendo que no es aconsejable dejar que siga un embarazo después de haber tomado mifepristona y/o misoprostol, ya que se desconocen los efectos completos de la mifepristona en el feto y la administración del misoprostol al principio del embarazo se ha asociado al desarrollo anormal del feto. Entiendo que el aborto después de la mifepristona/misoprostol tiene éxito en terminar el embarazo en aproximadamente el 95% de las mujeres tratadas. Cuando el aborto no es completo, se recomienda la aspiración al vació o la dilatación y curetaje para dejar de sangrar y evitar la anemia. ***Cuando no ocurre el aborto, se recomienda terminar el embarazo de forma quirúrgica debido al riesgo posible para el feto. Yo he estado de acuerdo de antemano con este procedimiento.***

No han habido problemas cardíacos graves en las 52,000 mujeres que han utilizado la combinación de drogas en el estudio sobre la terminación del embarazo. Sin embargo, ocurrieron complicaciones cardiovasculares graves, incluyendo un ataque al corazón mortal, durante abortos médicos utilizando una combinación de drogas diferente. Estos problemas cardíacos han ocurrido generalmente en mujeres que fuman mucho o que tienen gran cantidad de lípidos (grasas) en la sangre, diabetes, presión arterial alta o historia familiar de enfermedades del corazón. Este riesgo también aumentó en las mujeres mayores de 35 años de edad. Estas complicaciones sólo se han observado después de una prostaglandina inyectada y son raras (una en 20,000 casos). Hasta la fecha no hay pruebas que la prostaglandina oral (misoprostol) que yo tomaré en este estudio y que ha sido de amplio uso durante largos períodos de tiempo para el tratamiento de las úlceras estomacales, esté relacionada con esas reacciones cardiovasculares secundarias.

5. Declaración alterna

Se que se puede terminar mi embarazo pode medio de un aborto hecho por medio de cirugía (dilatación y curetaje o aspiración al vacío). Las posibles ventajas y desventajas de terminar el embarazo de forma quirúrgica en lugar de con medicamentos se me ha explicado. Las ventajas de terminar el embarazo de forma quirúrgica es que es un procedimiento de un día. Los riesgos relacionados con un aborto quirúrgico son mínimos. Esto incluye el riesgo del procedimiento anestésico. En los Estados Unidos, menos del 1% de las pacientes que se hacen un aborto quirúrgico tienen complicaciones graves relacionadas con el procedimiento tales como infección grave de la pelvis, cuello del útero rajado, sangre excesiva que necesite una transfusión o cirugía inesperada de mayor importancia (para una perforación del útero).

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OCT 27 1994

EVALUACION DE LA EFICACIA, SEGURIDAD Y ACEPTABILIDAD DE LA MIFEPRISTONA Y EL MISOPROSTOL PARA INDUCIR EL ABORTO EN LA MUJERES EN ESTADO DE EMBARAZO CON AMENORREA HASTA 63 DIAS DE DURACION

PROTOCOLO NUMERO 166 A

6. Declaración sobre lesiones físicas

Si necesito recibir tratamiento médico como resultado de una lesión física que ocurriera debido a mi participación en este estudio, se me ofrecerá la asistencia médica y tratamiento esencial a corto plazo de inmediato según lo determinen los médicos de este estudio sin cargo adicional ninguno para mi. No recibiré ninguna otra compensación monetaria para ninguna otra asistencia, pero tendré a mis disposición asesoramiento médico y servicios de referencia. Puedo obtener más información sobre la disponibilidad de la asistencia médica y tratamiento para cualquier lesión física que haya resultado de mi participación en este estudio del Investigador, Dr. Susan Haskell (teléfono:(515) 280-7000 or 1-(800) 568-2402).

7. A quién llamar en caso de emergencia

Comprendo que si sangro por el útero de forma excesiva o tengo dolores abdominales o si se me presenta cualquier otra emergencia médica, se lo informaré inmediatamente a (instituto, dirección, no. de teléfono). Además, me pondré en contacto con el Dr. Haskell (teléfono:(515) 280-7000). Si no me puedo poner en contacto con él o ella cuando exista una emergencia relacionada con el estudio, puedo ponerme en contacto con el _____ (teléfono:(515) 280-7000 or 1-(800) 568-2402).

8. Ofrecimiento de responder preguntas y libertad de retirarse del estudio.

Se me ha dicho que me puedo retirar del estudio en cualquier momento sin poner en peligro la asistencia médica que yo recibo o vaya a recibir en el futuro del hospital o la clínica. Si me retiro, se me ofrecerá un aborto quirúrgico. Se me ha dicho que me puedo poner en contacto con el Dr. Haskell (teléfono:(515) 280-7000) o el _____ (teléfono:(515) 280-7000) si tengo alguna pregunta sobre la investigación. Estos médicos pueden nombrar a sus asociados para que respondan mis preguntas.

También comprendo que el Investigador Principal me puede pedir que me retire del estudio si en su juicio clínico es de mejor interés para mi salud o si se me hace imposible seguir el procedimiento experimental de este estudio.

Yo comprendo que si mi tratamiento bajo el estudio no da como resultado un aborto, y si rehuso recibir un aborto quirúrgico y sigo con el embarazo, yo me arriesgo y la criatura puede tener el riesgo de complicaciones incluyendo deformidades del feto o de la criatura.

. Confidencialidad

Entiendo que la información obtenida en este estudio será transmitida de forma que no se pueda relacionar conmigo y que todos los récords se mantendrán en un gabinete con cierre. Comprendo que el Consejo sobre la Población (Population Council) o los observadores nombrados por ellos así como la Administración de Alimentos y Drogas de los Estados Unidos pueden solicitar el acceso a mis récords médicos.

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Dr. Susan C. Haskell CFN 19-34550
Des Moines, Iowa 50314
Exhibit 4 Page 15 of 49

Comprendo que se me puede solicitar que un representante del patrocinador me entreviste. Esta entrevista se llevará a cabo en el idioma que yo hablo y verificará que yo comprendo los riesgos, beneficios, procedimientos y naturaleza experimental del estudio. Si no estoy de acuerdo en ser entrevistada, esto no afectará mi asistencia médica actual o futura en el hospital o la clínica o mi participación en el estudio. Yo comprendo que puedo cambiar mi decisión en cualquier momento. Toda la información se mantendrá confidencial.

10. Declaración del sujeto

A mi, la infrascrita, se me han explicado los riesgos y beneficios de este estudio en un idioma que yo entiendo. Estoy de acuerdo en participar en este estudio como voluntaria.

_____

_____ _____

Fecha Firma de la voluntaria

11. Declaración del investigador

Yo, el infrascrito (la infrascrita) le explicado a la voluntaria en el idioma que ella habla, los procedimientos a seguir en este estudio y los riesgos y beneficios relacionados con éste.

_____ _____

Fecha Firma del(a) investigador(a)

_____ _____

Fecha Firma del testigo de las firmas anteriores y explicación

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EVALUACIÓN DE LA EFICACIA, SEGURIDAD Y ACEPTABILIDAD DE LA MIFEPRISTONA Y EL MISOPROSTOL PARA INDUCIR EL ABORTO EN LA MUJERES EN ESTADO DE EMBARAZO CON AMENORREA HASTA 63 DÍAS DE DURACIÓN

PROTOCOLO NUMERO 166 A

1. Propósito y objetivo del estudio

Es posible inducir el aborto en las mujeres que están embarazadas sin desearlo si toman mifepristona en combinación con una prostaglandina (misoprostol). La mifepristona es una droga que bloquea la acción de la progesterona, una hormona necesaria para mantener el embarazo. Una de las acciones de la mifepristona es la de interrumpir el embarazo en sus primeras etapas. Las prostaglandinas son substancias naturales creadas por el recubrimiento interior de la matriz durante la menstruación y que causan la contracción de la matriz. Durante las primeras etapas del embarazo, la mifepristona con misoprostol causan el aborto en, aproximadamente, el 95 por ciento de las mujeres. Las ventaja principal de este método de terminar el embarazo es que no se introducen instrumentos quirúrgicos en la matriz. Alrededor de 250,000 mujeres en 20 países han usado la mifepristona y una prostaglandina como un método médico para interrumpir el embarazo. La mifepristona y el misoprostol han sido utilizados por más de 50,000 mujeres en la dosis que se utilizará en este estudio. La dosificación que se va a estudiar ha sido aprobada en Francia para su uso de rutina por mujeres que tienen seis semanas o menos de embarazo. La mifepristona combinada con una prostaglandina también ha recibido aprobación para el uso en China, Gran Bretaña y Suecia. En los últimos dos países, la utilizan mujeres que tienen nueve semanas o menos de embarazo.

El objetivo del presente estudio es determinar la seguridad, eficacia y aceptabilidad de la mifepristona con misoprostol para terminar el embarazo en mujeres que hayan tenido el primer día de su último período mensual hace 63 días o menos. Tres grupos de mujeres con menos de 50 días; de 50 a 56 días y de 57 a 63 días desde el primer día del último período mensual se incluirán en el estudio. Este estudio se está llevando a cabo como un requisito para la registración de la mifepristona con misoprostol en la Administración de Alimentos y Medicinas de los Estados Unidos (Food and Drug Administration - FDA) para que estos productos se puedan usar para terminar embarazos en los Estados Unidos.

2. Visitas a la clínica

Tengo entendido que en mi primera visita (visita 1) seré asesorada sobre este método y se obtendrá una muestra de mi orina y sangre para asegurarse que estoy embarazada. Se me hará un examen médico, se examinará mi pelvis y tomarán mi historia clínica. Se determinará la duración de mi embarazo utilizando un ultrasonido vaginal, que es una sonda pequeña que se coloca dentro de la vagina. También, se me hará un análisis de sangre para ver si tengo el factor Rh en mi sangre. Si tengo el tipo de sangre Rh negativo, me pondrán una inyección durante la segunda visita para evitar que se desarrollen anticuerpos que pudiesen poner en peligro cualquier embarazo futuro. Para poder terminar mi embarazo, tomaré por vía oral tres tabletas de mifepristona (el primer medicamento) en presencia del personal del estudio.

Dos días después regresaré a la clínica (visita 2) aunque yo piense que he abortado y me tomaré por vía oral dos tabletas de misoprostol (segundo medicamento) si no he abortado. Si me tomo el segundo medicamento, la duración de mi estancia en la clínica durante la segunda visita será de aproximadamente cuatro horas. Durante ese tiempo seré cuidadosamente vigilada por el equipo del estudio. Durante este tiempo hay una oportunidad de un 60%-80% de que ocurra el aborto. Si vengo a la clínica en carro, me aseguraré de tener a alguien que me regrese a la casa después de esta visita. Entiendo que yo no puedo ir guiando hasta mi casa. Entiendo que si el aborto no ocurre en la clínica, ese muy probable que ocurra en la casa y puede que siga sangrando por el útero durante varios dias, parecido a una regla mensual fuerte. Debo usas almohadillas sanitarias hasta que deje de sangrar del útero o que las manchas terminen y no debo usar tampones. Al igual que con un aborto quirúrgico, no puedo volver a hacerme lavados vaginales ("douching") hasta que deje de sangrar (de 10-12 días). No debo volver a tener relaciones sexuales hasta después de ocho a diez días de haber tomado la prostaglandina, pues después de ese tiempo la mayoría de los abortos han terminado.

Yo entiendo que es posible que vea el producto de la concepción en la almohadilla sanitaria o en el excusado. Esto puede suceder en la clínica, en la casa o en el trabajo. Hasta la séptima semana después de la concepción este producto se llama un embrión; es más pequeño que una moneda de veinticinco centavos y generalmente está incrustado dentro de un coágulo de sangre. Aunque yo vea el producto de la concepción, no podré darme cuenta si el método ha tenido éxito ya que puede quedarse parte de la placenta en el útero. Por esto es importante regresar a la clínica para el seguimiento, la visita 3, para que los empleados de la clínica puedan determinar si el aborto ha sido completo.

Se me dará una cita para que regrese a la clínica dos semanas después de haber tomado la primera tableta (visita 3) para estar seguros que el tratamiento ha tenido efectividad. Si el tratamiento no ha tenido efectividad, entonces en ese momento se llevará a cabo un procedimiento quirúrgico llamado aspiración al vacío o dilatación y curetaje para terminar el aborto. Este es el mismo procedimiento quirúrgico que hubiese recibido si hubiese decidido hacerme un aborto quirúrgico desde el principio. Estaré segura de tener a alguien que me lleve para la casa en carro después de esta visita y entiendo que yo misma no puedo manejar. Si me doy cuenta que después del tratamiento tengo un flujo vaginal que tiene olor, puede indicar una infección. Me pondré en contacto con mi médico para hacer una cita.

Entiendo que la sangre puede continuar después de mi tercera visita. Si esto sucede, la clínica se pondrá en contacto telefónico conmigo para determinar si ya ha parado o si necesito tratamiento adicional.

Yo entiendo que hasta ahora no ha habido indicaciones que el uso una antiprogestina para terminar un embarazo no ha evitado ni ha dañado la capacidad de una mujer de tener un bebé en el futuro. La mujeres que han tomado mifepristona han podido concebir después y han tenido hijos saludables. Ya que es posible volver a quedar embarazada después del aborto, se me pedirá que seleccione un método para evitar los hijos.

3. Beneficios

Entiendo que la ventaja del método para terminar un embarazo utilizando mifepristona/misoprostol es que evita un procedimiento quirúrgico. No hay riesgos relacionados con la anestesia no riesgo de perforación del útero o de lesiones al conducto cervical que ocurre raras veces después de terminar un embarazo de forma quirúrgica. Otro beneficio es la satisfacción de participar en el estudio que hará que las mujeres de los Estado Unidos tengan disponibles la mifepristona/misoprostol.

4. Riesgos y molestias

Entiendo que cuando me saquen la sangre para los análisis en la primera visita puedo sentir molestia, tener moretones y puede ocurrir una infección en el sitio de donde se sacó la sangre. Entiendo que la experiencia que existe hasta ahora con la combinación de drogas y el terminar un embarazo de poco tiempo indica que esta terapia tiene pocas reacciones secundarias. La frecuencia de complicaciones de corta duracion se puede comparar con la que se observa después de un aborto quirúrgico hecho con aspiración al vacío. La queja más común durante el tratamiento (en particular después de la administración del segundo medicamento) es dolor en el bajo vientre o retorcijones parecidos a los que se relacionan con un período mensual fuerte. Recibiré el medicamento apropiado contra el dolor cuando sea necesario. Entiendo que no debo tomar aspirina, Motrin®, ibuprofen (Advil®) o cualquier otra droga que se sabe bloque la acción de las prostaglandinas. Sin embargo, puedo tomar Tylenol® y mi médico me puedo recetar medicamentos más fuertes contra el dolor. Entiendo que los retorcijones y los dolores abdominales es una parte del proceso del aborto normal y esperada. Se ha observado la existencia de nauseas, vómitos y diarrea después de la administración del segundo medicamento. Por lo tanto, es necesario quedarse en la clínica bajo la supervisión apropiada en la segunda visita durante alrededor de cuatro horas antes de regresar a la casa. Se puede esperar sangre del útero, parecida a una menstruación fuerte y de una semana de duración. En raras ocasiones, puede haber mucha sangre del útero que cause la necesidad de hacer un aborto quirúrgico y/o una transfusión de sangre.

Entiendo que no es aconsejable dejar que siga un embarazo después de haber tomado mifepristona y/o misoprostol, ya que se desconocen los efectos completos de la mifepristona en el feto y la administración del misoprostol al principio del embarazo se ha asociado al desarrollo anormal del feto. Entiendo que el aborto después de la mifepristona/misoprostol tiene éxito en terminar el embarazo en aproximadamente el 95% de las mujeres tratadas. Cuando el aborto no es completo, se recomienda la aspiración al vació o la dilatación y curetaje para dejar de sangrar y evitar la anemia. ***Cuando no ocurre el aborto, se recomienda terminar el embarazo de forma quirúrgica debido al riesgo posible para el feto. Yo he estado de acuerdo de antemano con este procedimiento.***

No han habido problemas cardíacos graves en las 52,000 mujeres que han utilizado la combinación de drogas en el estudio sobre la terminación del embarazo. Sin embargo, ocurrieron complicaciones cardiovasculares graves, incluyendo un ataque al corazón mortal, durante abortos médicos utilizando una combinación de drogas diferente. Estos problemas cardíacos han ocurrido generalmente en mujeres que fuman mucho o que tienen gran cantidad de lípidos (grasas) en la sangre, diabetes, presión arterial alta o historia familiar de enfermedades del corazón. Este riesgo también aumentó en las mujeres mayores de 35 años de edad. Estas complicaciones sólo se han observado después de una prostaglandina inyectada y son raras (una en 20,000 casos). Hasta la fecha no hay pruebas que la prostaglandina oral (misoprostol) que yo tomaré en este estudio y que ha sido de amplio uso durante largos períodos de tiempo para el tratamiento de las úlceras estomacales, esté relacionada con esas reacciones cardiovasculares secundarias.

5. Declaración alterna

Se que se puede terminar mi embarazo pode medio de un aborto hecho por medio de cirugía (dilatación y curetaje o aspiración al vacío). Las posibles ventajas y desventajas de terminar el embarazo de forma quirúrgica en lugar de con medicamentos se me ha explicado. Las ventajas de terminar el embarazo de forma quirúrgica es que es un procedimiento de un día. Los riesgos relacionados con un aborto quirúrgico son mínimos. Esto incluye el riesgo del procedimiento anestésico. En los Estados Unidos, menos del 1% de las pacientes que se hacen un aborto quirúrgico tienen complicaciones graves relacionadas con el procedimiento tales como infección grave de la pelvis, cuello del útero rajado, sangre excesiva que necesite una transfusión o cirugía inesperada de mayor importancia (para una perforación del útero).

6. Declaración sobre lesiones físicas

Si necesito recibir tratamiento médico como resultado de una lesión física que ocurriera debido a mi participación en este estudio, se me ofrecerá la asistencia médica y tratamiento esencial a corto plazo de inmediato según lo determinen los médicos de este estudio sin cargo adicional ninguno para mi. No recibiré ninguna otra compensación monetaria para ninguna otra asistencia, pero tendré a mis disposición asesoramiento médico y servicios de referencia. Puedo obtener más información sobre la disponibilidad de la asistencia médica y tratamiento para cualquier lesión física que haya resultado de mi participación en este estudio del Investigador, Dr. Susan Haskell (teléfono:(515) 280-7000 or 1-(800) 568-2402).

7. A quién llamar en caso de emergencia

Comprendo que si sangro por el útero de forma excesiva o tengo dolores abdominales o si se me presenta cualquier otra emergencia médica, se lo informaré inmediatamente a (instituto, dirección, no. de teléfono). Además, me pondré en contacto con el Dr. Haskell (teléfono:(515) 280-7000). Si no me puedo poner en contacto con él o ella cuando exista una emergencia relacionada con el estudio, puedo ponerme en contacto con el _____ (teléfono:(515) 280-7000 or 1-(800) 568-2402).

8. Ofrecimiento de responder preguntas y libertad de retirarse del estudio.

Se me ha dicho que me puedo retirar del estudio en cualquier momento sin poner en peligro la asistencia médica que yo recibo o vaya a recibir en el futuro del hospital o la clínica. Si me retiro, se me ofrecerá un aborto quirúrgico. Se me ha dicho que me puedo poner en contacto con el Dr. Haskell (teléfono:(515) 280-7000) o el _____ (teléfono:(515) 280-7000) si tengo alguna pregunta sobre la investigación. Estos médicos pueden nombrar a sus asociados para que respondan mis preguntas.

También comprendo que el Investigador Principal me puede pedir que me retire del estudio si en su juicio clínico es de mejor interés para mi salud o si se me hace imposible seguir el procedimiento experimental de este estudio.

Yo comprendo que si mi tratamiento bajo el estudio no da como resultado un aborto, y si rehuso recibir un aborto quirúrgico y sigo con el embarazo, yo me arriesgo y la criatura puede tener el riesgo de complicaciones incluyendo deformidades del feto o de la criatura.

9. Confidencialidad

Entiendo que la información obtenida en este estudio será transmitida de forma que no se pueda relacionar conmigo y que todos los récords se mantendrán en un gabinete con cierre. Comprendo que el Consejo sobre la Población (Population Council) o los observadores nombrados por ellos así como la Administración de Alimentos y Drogas de los Estados Unidos pueden solicitar el acceso a mis récords médicos.

Comprendo que se me puede solicitar que un representante del patrocinador me entreviste. Esta entrevista se llevará a cabo en el idioma que yo hablo y verificará que yo comprendo los riesgos, beneficios, procedimientos y naturaleza experimental del estudio. Si no estoy de acuerdo en ser entrevistada, esto no afectará mi asistencia médica actual o futura en el hospital o la clínica o mi participación en el estudio. Yo comprendo que puedo cambiar mi decisión en cualquier momento. Toda la información se mantendrá confidencial.

10. Declaración del sujeto

A mi, la infrascrita, se me han explicado los riesgos y beneficios de este estudio en un idioma que yo entiendo. Estoy de acuerdo en participar en este estudio como voluntaria.

_____

_____ _____

Fecha Firma de la voluntaria

11. Declaración del investigador

Yo, el infrascrito (la infrascrita) le explicado a la voluntaria en el idioma que ella habla, los procedimientos a seguir en este estudio y los riesgos y beneficios relacionados con éste.

_____ _____

Fecha Firma del(a) investigador(a)

_____ _____

Fecha Firma del testigo de las firmas anteriores y explicación

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Hai ngày sau, tôi sẽ trở lại bệnh viện (khám bệnh 2) cả khi tôi tin rằng tôi đã phá thai rồi và tôi sẽ uống hai viên misoprostol (cho uống thuốc lần thứ hai) nếu tôi chưa phá thai. Nếu tôi uống thuốc lần thứ hai, thời gian tôi ở lại bệnh viện lần thứ hai sẽ dài chừng khoảng bốn giờ, trong khi đó tôi sẽ được theo dõi thật sát bởi nhóm nghiên cứu. Trong thời gian này, có chừng 60-80% cơ may phá thai sẽ xảy ra. Nếu tôi đến bệnh viện bằng xe, tôi sẽ chắc chắn sắp xếp để cho một người nào khác lái xe cho tôi về nhà từ lần khám bệnh này, và tôi hiểu rằng tôi sẽ không tự mình lái xe về nhà. Tôi hiểu rằng nếu sự phá thai không xảy ra tại bệnh viện, thì rất có thể nó sẽ xảy ra tại nhà và tôi có thể bị tiếp tục chảy máu tử cung giống như thời kỳ kinh nguyệt nặng trong nhiều ngày. Tôi sẽ dùng băng kinh nguyệt cho đến khi máu chảy từ tử cung hay máu chảy nhẹ từ âm đạo chấm dứt và không dùng nút bông kinh nguyệt. Cũng như với việc phá thai qua giải phẫu, tôi không thể xối nước lại cho đến khi máu ngưng rỉ (vào khoảng từ 10-12 ngày). Tôi sẽ không làm tình lại trong khoảng từ 8 đến 10 ngày sau khi uống protaglandin mà vào thời gian hầu hết các vụ phá thai đều đã được hoàn thành.

Tôi hiểu rằng tôi có thể thấy sản phẩm của sự thai nghén trên băng vệ sinh hay trong cầu vệ sinh. Điều này có thể xảy ra tại bệnh viện, tại nhà, hay tại sở làm. Cho đến hết tuần thứ bảy sau khi thai nghén, sản phẩm này được gọi là bào thai; nó nhỏ hơn đồng 25 xu và thường thường được lồng trong các cục máu. Dù cho tôi có nhìn thấy sản phẩm thai nghén, tôi sẽ không thể nào nói được rằng phương pháp này có hiệu quả hay không vì một phần của nhau có thể còn ở lại trong tử cung. Vì vậy mà tôi cần phải trở lại bệnh viện để được theo dõi, khám bệnh 3, để nhân viên bệnh viện có thể xác định là phá thai đã hoàn thành hay chưa.

Một buổi hẹn sau này sẽ được dự trù để cho tôi trở lại bệnh viện hai tuần sau khi uống viên đầu tiên (khám bệnh 3), để bảo đảm rằng việc chữa trị có hiệu quả. Nếu việc chữa trị không có hiệu quả, thì một thủ tục gọi là hút chân không hay việc làm dãn nở và nạo tử cung sẽ được thực hiện để hoàn thành việc phá thai vào lúc đó. Đây cũng giống như thủ tục giải phẫu đáng lẽ đã được thực hiện nếu ngay lúc đầu tôi đã chọn đi theo cách phá thai bằng giải phẫu. Tôi sẽ chắc chắn sắp xếp cho người nào đó lái xe cho tôi về nhà từ lần khám này, và hiểu rằng tôi sẽ không tự lái xe về nhà. Nếu tôi thấy mủ hay huyết trắng từ âm đạo có mùi hôi sau khi chữa trị, điều này có thể chỉ ra một sự nhiễm trùng. Tôi sẽ tiếp xúc với y sĩ để làm hẹn khám.

Tôi hiểu rằng máu chảy có thể tiếp tục qua cả lần khám thứ ba của tôi. Nếu điều này xảy ra, bệnh viện sẽ tiếp xúc với tôi bằng điện thoại để xác định xem máu đã ngừng chảy chưa hay tôi cần phải được chữa trị thêm.

LƯỢNG GIÁ VỀ CÔNG HIỆU, AN TOÀN, VÀ TÍNH CHẤP NHẬN ĐƯỢC CỦA MIFEPRISTONE VÀ MISOPROSTOL TRONG VIỆC GÂY PHÁ THAI NƠI PHỤ NỮ MANG THAI ĐÃ TẮT KINH TỚI 63 NGÀY

KẾ HOẠCH THÍ NGHIỆM CHI TIẾT SỐ: 166 A

1. Mục đích và các mục tiêu của việc nghiên cứu

Rất có thể gây phá thai nơi phụ nữ có thai mà không muốn có con bằng cách cho dùng mifepristone kết hợp với một prostaglandin (misoprostol). Mifepristone là một loại thuốc ngăn chặn hoạt động của kích thích tố tiết ra bởi noãn sào, một loại kích thích tố cần có để duy trì sự thai nghén. Một trong những hoạt động của Mifepristone là làm gián đoạn sự thai nghén trong các thời kỳ đầu. Prostaglandins là các chất tự nhiên do lớp lót của tử cung sản xuất ra trong lúc có kinh và gây ra sự co rút của tử cung. Trong các thời kỳ đầu của sự thai nghén, mifepristone cộng với misoprostol gây ra phá thai trong khoảng 95 phần trăm phụ nữ. Các lợi ích chính của phương pháp chấm dứt thai nghén này là không cần phải có dụng cụ giải phẫu đẩy vào trong tử cung. Khoảng 250,000 phụ nữ trong 20 nước đã dùng mifepristone và một prostaglandin như một phương pháp y học để chấm dứt thai nghén. Mifepristone và misoprostol đã được trên 50,000 phụ nữ sử dụng ở liều lượng được dùng trong cuộc nghiên cứu này. Liều lượng được nghiên cứu đã được chấp thuận tại Pháp để dùng theo thông lệ cho phụ nữ có thai trong bảy tuần lễ hay ít hơn. Mifepristone phối hợp cùng với prostaglandin cũng đã được chấp thuận cho dùng tại Trung quốc, Anh quốc, và Thụy điển. Tại hai nước sau này, nó được dùng cho phụ nữ có thai trong chín tuần hay ít hơn.

Các mục tiêu của cuộc nghiên cứu hiện nay là xác định tính an toàn, công hiệu, và chấp nhận được của mifepristone cộng với misoprostol để chấm dứt thai nghén nơi phụ nữ đã được tắt kinh tới 63 ngày hay ít hơn kể từ ngày đầu của kỳ kinh nguyệt trước. Ba nhóm phụ nữ có thai, một nhóm ít hơn 50 ngày; một nhóm từ 50 đến 56 ngày; và từ 57 đến 63 ngày kể từ ngày đầu của kỳ kinh nguyệt trước được đưa vào nghiên cứu này. Cuộc nghiên cứu đang được hoàn thành này là một điều kiện để đăng ký thuốc mifepristone cộng misoprostol với Cơ quan Quản Trị Thực phẩm và Thuốc(FDA) để cho các sản phẩm này có thể được dùng để chấm dứt thai nghén tại Hoa kỳ.

2. Khám bệnh để quan sát.

Tôi hiểu rằng vào lần khám bệnh đầu tiên (khám bệnh 1) tôi sẽ nhận được các lời khuyên về phương pháp, và một mẫu nước tiểu và máu sẽ được lấy để chắn chắn rằng tôi đang mang thai. Tôi sẽ được khám sức khỏe, và khám xương chậu, và bệnh sử của tôi được ghi lại. Nhờ dùng một máy dò siêu âm đặt vào âm đạo, thời gian tôi mang thai sẽ được xác định. Tôi cũng sẽ được thử máu để tìm yếu tố Rh trong máu của tôi. Nếu tôi có loại máu với Rh âm, tôi sẽ được chích một mũi thuốc vào lần khám bệnh thứ hai để phòng ngừa sự phát sinh những kháng thể có thể làm nguy hại đến sự thai nghén trong tương lai. Để chấm dứt sự thai nghén của tôi, tôi sẽ uống ba viên mifepristone (lần cho uống thuốc đầu tiên) trước mặt các nhân viên của cuộc nghiên cứu.

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Hai ngày sau, tôi sẽ trở lại bệnh viện (khám bệnh 2) cả khi tôi tin rằng tôi đã phá thai rồi và tôi sẽ uống hai viên misoprostol (cho uống thuốc lần thứ hai) nếu tôi chưa phá thai. Nếu tôi uống thuốc lần thứ hai, thời gian tôi ở lại bệnh viện lần thứ hai sẽ dài chừng khoảng bốn giờ, trong khi đó tôi sẽ được theo dõi thật sát bởi nhóm nghiên cứu. Trong thời gian này, có chừng 60-80% cơ may phá thai sẽ xảy ra. Nếu tôi đến bệnh viện bằng xe, tôi sẽ chắc chắn sắp xếp để cho một người nào khác lái xe cho tôi về nhà từ lần khám bệnh này, và tôi hiểu rằng tôi sẽ không tự mình lái xe về nhà. Tôi hiểu rằng nếu sự phá thai không xảy ra tại bệnh viện, thì rất có thể nó sẽ xảy ra tại nhà và tôi có thể bị tiếp tục chảy máu từ cung giống như thời kỳ kinh nguyệt nặng trong nhiều ngày. Tôi sẽ dùng băng kinh nguyệt cho đến khi máu chảy từ tử cung hay máu chảy nhẹ từ âm đạo chấm dứt và không dùng nút bông kinh nguyệt. Cũng như với việc phá thai qua giải phẫu, tôi không thể xối nước lại cho đến khi máu ngưng rỉ (vào khoảng từ 10-12 ngày). Tôi sẽ không làm tình lại trong khoảng từ 8 đến 10 ngày sau khi uống protaglandin mà vào thời gian hầu hết các vụ phá thai đều đã được hoàn thành.

Tôi hiểu rằng tôi có thể thấy sản phẩm của sự thai nghén trên băng vệ sinh hay trong cầu vệ sinh. Điều này có thể xảy ra tại bệnh viện, tại nhà, hay tại sở làm. Cho đến hết tuần thứ bảy sau khi thai nghén, sản phẩm này được gọi là bào thai; nó nhỏ hơn đồng 25 xu và thường thường được lồng trong các cục máu. Dù cho tôi có nhìn thấy sản phẩm thai nghén, tôi sẽ không thể nào nói được rằng phương pháp này có hiệu quả hay không vì một phần của nhau có thể còn ở lại trong tử cung. Vì vậy mà tôi cần phải trở lại bệnh viện để được theo dõi, khám bệnh 3, để nhân viên bệnh viện có thể xác định là phá thai đã hoàn thành hay chưa.

Một buổi hẹn sau này sẽ được dự trù để cho tôi trở lại bệnh viện hai tuần sau khi uống viên đầu tiên (khám bệnh 3), để bảo đảm rằng việc chữa trị có hiệu quả. Nếu việc chữa trị không có hiệu quả, thì một thủ tục gọi là hút chân không hay việc làm dãn nở và nạo tử cung sẽ được thực hiện để hoàn thành việc phá thai vào lúc đó. Đây cũng giống như thủ tục giải phẫu đáng lẽ đã được thực hiện nếu ngay lúc đầu tôi đã chọn đi theo cách phá thai bằng giải phẫu. Tôi sẽ chắc chắn sắp xếp cho người nào đó lái xe cho tôi về nhà từ lần khám này, và hiểu rằng tôi sẽ không tự lái xe về nhà. Nếu tôi thấy mủ hay huyết trắng từ âm đạo có mùi hôi sau khi chữa trị, điều này có thể chỉ ra một sự nhiễm trùng. Tôi sẽ tiếp xúc với y sĩ để làm hẹn khám.

Tôi hiểu rằng máu chảy có thể tiếp tục qua cả lần khám thứ ba của tôi. Nếu điều này xảy ra, bệnh viện sẽ tiếp xúc với tôi bằng điện thoại để xác định xem máu đã ngừng chảy chưa hay tôi cần phải được chữa trị thêm.

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KẾ HOẠCH THÍ NGHIỆM CHI TIẾT SỐ: 166 A

Tôi hiểu rằng không có một dấu chỉ nào hiện thời cho thấy rằng việc dùng một chất antiprogestin để chấm dứt sự mang thai đã ngăn ngừa hay làm phương hại đến khả năng có con của người phụ nữ trong tương lai. Phụ nữ uống mifepristone đã có thể có khả năng thụ thai và rồi sau đó có con khỏe mạnh. Vì rất có thể có thai lại sau khi phá thai, tôi được yêu cầu phải chọn và dùng một phương pháp ngừa thai nào đó.

3. Các Lợi ích.

Tôi hiểu rằng một lợi ích của phương pháp y học dùng mifepristone/misoprostol để chấm dứt thai nghén là nó tránh được thủ tục giải phẫu. Không có rủi ro liên hệ đến thuốc mê hay rủi ro tử cung bị lủng hay thương tích ở vùng cổ tử cung hiếm hoi quan sát thấy sau khi chấm dứt thai nghén bằng phẫu thuật. Một lợi ích khác là sự hài lòng được tham gia vào cuộc nghiên cứu có thể làm cho mifepristone/misoprostol sẵn sàng để sử dụng cho phụ nữ tại Hoa kỳ.

4. Các rủi ro và khó chịu

Tôi hiểu rằng lấy máu để thử nghiệm vào lần khám bệnh đầu tiên có thể gây ra khó chịu, bầm tím, và cũng có thể nhiễm trùng tại nơi lấy máu. Tôi hiểu rằng kinh nghiệm thu lượm được cho đến bây giờ trong việc phối hợp thuốc và chấm dứt thai nghén sớm cho thấy phép trị liệu này có rất ít biến chứng. Tính thường xảy ra của các biến chứng ngắn hạn này có thể so sánh được với tính thường xảy ra của các biến chứng quan sát được sau khi phá thai bằng phẫu thuật qua việc dùng hút chân không. Điều than phiền thông thường nhất trong khi chữa trị (nhất là sau khi cho uống thuốc lần thứ hai) là đau ở bụng dưới hay co quắp bắp thịt cũng giống như co quắp liên hệ với một thời kỳ kinh nguyệt nặng. Tôi sẽ nhận được thuốc men thích hợp để chống đau khi cần. Tôi hiểu rằng tôi sẽ không uống thuốc as-pi-rin, Mo-trin*, I-bu-pro-fen (Advil*) hay bất cứ một thứ thuốc gì khác được biết có tác dụng làm tắc nghẽn hoạt động của các prostaglandins. Tuy nhiên, tôi sẽ uống Ty-le-nol* và tôi có thể nhận được từ bác sĩ một liều lượng mạnh hơn để chống đau. Tôi hiểu rằng co quắp bắp thịt và đau bụng dưới là thông thường và là một phần của tiến trình phá thai. Buồn nôn, mửa, và ỉa chảy đã được quan sát thấy tiếp theo lần cho uống thuốc thứ hai. Vì vậy, vào lần khám bệnh thứ hai, tôi cần phải ở lại bệnh viện dưới sự giám sát y tế vào khoảng bốn giờ trước khi trở về nhà. Chảy máu âm đạo, cũng giống như trong kỳ kinh nguyệt nặng và dài ít nhất một tuần, có thể xảy ra. Trong những trường hợp hiếm hoi, chảy máu âm đạo nặng có thể xảy ra đòi hỏi phải phá thai bằng phẫu thuật và/hay truyền máu.

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KẾ HOẠCH THÍ NGHIỆM CHI TIẾT SỐ: 166 A

Tôi hiểu rằng không nên cho để cho việc thai nghén tiếp tục sau khi dùng mifepristone và/hay misoprostol, vì hiệu quả đầy đủ của mifepristone trên thai nhi không được biết và việc cho thuốc misoprostol vào lúc mới thai nghén đã được liên kết với việc phát triển các thai nhi bất bình thường. Tôi hiểu rằng phá thai sau khi uống mifepristone/misoprostol đã thành công trong việc chấm dứt thai nghén trong 95% số phụ nữ được chữa trị. Khi phá thai không hoàn tất, hút chân không hay làm dãn nở và nạo tử cung được khuyến cáo để chấm dứt chảy máu và ngăn ngừa thiếu máu. *Khi phá thai không xảy ra, chấm dứt thai nghén bằng phẫu thuật được khuyến cáo bởi vì có sự rủi ro cho thai nhi. Tôi đã đồng ý trước đây về thủ tục này.*

Không có tình trạng tim nghiêm trọng nào trong số 52,000 phụ nữ dùng sự phối hợp thuốc trong thí nghiệm này để chấm dứt thai nghén. Tuy nhiên, có biến chứng nghiêm trọng về tim mạch, kể cả một trường hợp chết vì đau tim trong khi phá thai theo cách y học dùng phối hợp thuốc. Các tình trạng về tim này thường xảy ra nơi phụ nữ hút thuốc nặng hay đã tăng lượng mỡ trong máu, tiểu đường, áp huyết cao, hay có truyền thống bệnh tim trong gia đình. Rủi ro này cũng tăng lên với phụ nữ trên 35 tuổi. Các biến chứng này đã chỉ thấy sau khi chích prostaglandin và rất hiếm xảy ra (một trong 20,000 trường hợp). Cho đến nay không có bằng chứng nào rằng uống prostaglandin (misoprostol) được liên kết với biến chứng về tim mạch mà tôi sẽ uống trong cuộc nghiên cứu này và đã được sử dụng rộng rãi trong những thời gian dài trong để phòng ngừa bao tử bị ung loét.

5. Phát biểu về Cách khác

Tôi biết rằng thai nghén của tôi có thể chấm dứt bằng thủ tục phá thai theo phẫu thuật (làm dãn nở và và nạo vét tử cung hay hút chân không). Những lợi ích và bất lợi có thể có của việc chấm dứt thai nghén bằng phẫu thuật thay vì chấm dứt bằng y học đã được cắt nghĩa cho tôi hiểu. Lợi ích của việc chấm dứt thai nghén bằng phẫu thuật là thủ tục chỉ kéo dài trong 1 ngày. Các rủi ro liên kết với phá thai bằng phẫu thuật là tối thiểu. Các rủi ro này gồm cả rủi ro dùng thuốc mê. Tại Hoa kỳ, chỉ có dưới 1% các bệnh nhân dùng thủ tục phá thai bằng phẫu thuật trải qua một biến chứng quan trọng liên kết với thủ tục này như nhiễm độc nghiêm trọng vùng xương chậu, cổ tử cung bị rách, chảy máu cần phải truyền máu hay phẫu thuật mà không có ý định trước (vì tử cung bị lủng).

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6. Phát biểu về Thương tích gây cho thân thể

Nếu tôi cần phải chữa trị bằng thuốc men vì hậu quả của thương tích về thân thể phát sinh từ việc tôi tham gia vào việc nghiên cứu này, việc chăm sóc thuốc men và chữa trị ngắn hạn, thiết yếu, tức thời như được xác định bởi các y sĩ trong cuộc nghiên cứu này sẽ có sẵn cho tôi mà không gây tổn phí. Sẽ không có một sự đền bù tiền bạc nào cho bất cứ sự chăm sóc nào khác, nhưng việc tham khảo về y tế và các dịch vụ giới thiệu thích hợp vẫn có sẵn. Muốn biết thêm chi tiết về các sự chăm sóc về y tế và chữa trị có sẵn cho thương tích do hậu quả của việc tôi tham gia vào cuộc nghiên cứu này, xin tiếp xúc với chuyên viên nghiên cứu, Bác sĩ Susan Haskell (điện thoại (515) 280-700) hay (1-800) 568-2404.

7. Gọi Ai trong Trường hợp Khẩn cấp

Tôi hiểu rằng nếu tử cung chảy máu nghiêm trọng, hay đau bụng dưới, hay các trường hợp y tế khẩn cấp khác phát sinh từ sự liên kết với phương pháp này, tôi sẽ báo cáo ngay lập tức cho Chương trình Planned Parenthood of Greater Iowa, 851 19th Street, Des Moines, IA 50314. Thêm nữa, tôi sẽ tiếp xúc với Bác sĩ Haskell (điện thoại số (515) 280-7000. Nếu không thể tiếp xúc được với ông hay bà ta trong trường hợp khẩn cấp liên quan đến cuộc nghiên cứu này, tôi sẽ tiếp xúc với ———————— tại số (515) 280-7000 hay (1-800) 568-2404.

8. Đề nghị Trả lời Câu hỏi và Tự do Rút lui khỏi cuộc Nghiên cứu.

Tôi đã được cho biết rằng tôi có thể rút lui khỏi cuộc nghiên cứu này bất cứ lúc nào mà không làm nguy hại đến sự chăm sóc y tế của bệnh viện trong hiện tại hay tương lai cho tôi. Nếu tôi rút lui tôi sẽ được đề nghị phá thai bằng phẫu thuật. Tôi đã được cho biết để tiếp xúc với Bác sĩ Haskell Điện thoại: (515) 280-7000 hay ———————— Điện thoại : (515) 280-7000 nếu tôi có câu hỏi về cuộc nghiên cứu. Các y sĩ này có thể chỉ định các cộng sự viên để trả lời những câu hỏi của tôi.

Tôi cũng hiểu rằng chuyên viên nghiên cứu chính có thể đòi hỏi tôi rút lui khỏi cuộc nghiên cứu này, nếu theo ý kiến về y khoa của ông hay bà ta việc này tốt nhất cho sức khỏe của tôi hay nếu tôi không thể theo các thủ tục thử nghiệm của cuộc nghiên cứu này nữa.

Tôi hiểu rằng, nếu việc chữa trị cho tôi trong cuộc nghiên cứu này không đem lại kết quả phá thai, và nếu tôi từ khước phá thai bằng phẫu thuật và tiếp tục với việc thai nghén, tôi phải chịu rủi ro và đứa trẻ phải chịu rủi ro, về các biến chứng kể cả thai nhi hay trẻ sơ sinh dị dạng.

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9. Kín đáo

Tôi hiểu rằng các chi tiết có được trong cuộc nghiên cứu này sẽ được chuyển đi dưới một hình thức không thể nhận diện ra tôi, và rằng tất cả các hồ sơ sẽ được giữ trong tủ khóa. Tôi hiểu rằng Hội đồng Dân số hay những người được chỉ định theo dõi, cũng như Sở Quản trị Thực phẩm và Thuốc men của Hoa kỳ có thể yêu cầu tìm đến hồ sơ y bạ của tôi.

10. Phát biểu về Đối tượng

Tôi, ký tên dưới đây , đã đã được cắt nghĩa về những rủi ro và lợi ích trong cuộc nghiên cứu này bằng một ngôn ngữ mà tôi hiểu được. Tôi đồng ý tham gia vào cuộc nghiên cứu này như một đối tượng tình nguyện.

_____ _____

Ngày tháng Chữ ký của người tình nguyện

11. Phát biểu của Chuyên viên Nghiên cứu

Tôi, ký tên dưới đây, đã giải thích cho người tình nguyện bằng ngôn ngữ mà họ nói về thủ tục phải theo trong cuộc nghiên cứu này cùng các rủi ro và lợi ích liên quan.

_____ _____

Ngày tháng Chữ ký của chuyên viên nghiên cứu

_____ _____

Ngày tháng Chữ lý của chứng nhân cho các chữ ký và giải thích trên

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EVALUACIÓN DE LA EFICACIA, SEGURIDAD Y ACEPTABILIDAD DE LA MIFEPRISTONA Y EL MISOPROSTOL PARA INDUCIR EL ABORTO EN LA MUJERES EN ESTADO DE EMBARAZO CON AMENORREA HASTA 63 DÍAS DE DURACIÓN

PROTOCOLO NUMERO 166 A

1. Propósito y objetivo del estudio

Es posible inducir el aborto en las mujeres que están embarazadas sin desearlo si toman mifepristona en combinación con una prostaglandina (misoprostol). La mifepristona es una droga que bloquea la acción de la progesterona, una hormona necesaria para mantener el embarazo. Una de las acciones de la mifepristona es la de interrumpir el embarazo en sus primeras etapas. Las prostaglandinas son substancias naturales creadas por el recubrimiento interior de la matriz durante la menstruación y que causan la contracción de la matriz. La información obtenida recientmente apoya las declaraciones que la mifepristona más misoprostol pueden causar el aborto en aproximadamente el 95 por ciento de las mujeres que tuvieron el primer día de su última menstruación no más de 49 días antes de recibir la mifepristona. Entre las mujeres que tuvieron el primer día de su última menstruación de 50 a 63 días antes de recibir la mifepristona, tantas como una de cada cuatro pueden necesitar algún tipo de intervención quirúrgica según sugiere esta nueva información. hay una serie de razones por las cuales puede ser necesaria dicha intervención quirúrgica incluyendo la continuación del embarazo, aborto incompleto o exceso de sangramiento. La posibilidad del exceso de sangramiento aumenta con el aumento en la duración de la amenorrea.** Las ventaja principal de este método de terminar el embarazo es que no se introducen instrumentos quirúrgicos en la matriz. Alrededor de 150,000 mujeres en 20 países han usado la mifepristona y una prostaglandina como un método médico para interrumpir el embarazo. La mifepristona y el misoprostol han sido utilizados por más de 50,000 mujeres en la dosis que se utilizará en este estudio. La dosificación que se va a estudiar ha sido aprobada en Francia para su uso de rutina por mujeres que tienen seis semanas o menos de embarazo. La mifepristona combinada con una prostaglandina también ha recibido aprobación para el uso en China, Gran Bretaña y Suecia. En los últimos dos países, la utilizan mujeres que tienen nueve semanas o menos de embarazo.

**Enmienda 3 de fecha 2 de mayo de 1995

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