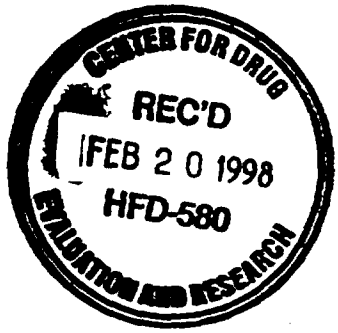
Population Council

noted 2/27/98

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CORRESP



2/23/00

February 19, 1998

VIA FEDERAL EXPRESS

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

no def
2/19/00

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE 2/20

RE: NDA 20-687, MIFEPRISTONE 200 MG ORAL TABLETS
AMENDMENT 013 - CONFIRMATION AND DOCUMENTATION
FOR MEETING MARCH 16, 1998 - 2:00 p.m.-3:30 p.m.

Dear

This letter confirms our arrangements to attend the March 16, 1998 (2:00 p.m. - 3:30 p.m.) meeting you have scheduled in response to our January 30, 1998 letter. We appreciate your timely response and the availability of the Division staff for this meeting.

The Agenda for the meeting was presented in the January 30 letter and remains current as restated below:

FINAL AGENDA

I. Plan for amending NDA to include new bulk drug substance manufacturer:
   - A. Discussion of FDA's assessment of the CMC from Gedeon Richter and use of their pilot batches as standards,
   - B. Discussion of demonstrating comparability to Gedeon Richter bulk drug substance given the perceived differences from the Roussel process,
   - C. Discussion of demonstrating comparability of the new bulk drug substance to the Roussel material.

II. Discussion of the possible use of Gedeon Richter pilot batches for compassionate patient use in the United States.

III. Discussion of the use of 200 mg mifepristone plus higher prostaglandin dosages being studied by others versus the existing NDA dosages. What type of clinical data would be required for the Population Council/NeoGen to amend its NDA for use of these lower dosages?

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

As you may remember, at our meeting on August 11, 1997 we sought your concurrence to use the pilot batches of Gedeon Richter bulk drug substance as a "gold standard," to validate a future manufacturer(s), particularly as no drug substance was available from Roussel. The information on manufacturing provided by Gedeon Richter was submitted for your review in prior amendments in 1997.

During that meeting, we discussed efforts to secure bulk drug substance from Roussel. The Population Council has a small quantity of bulk drug substance from Roussel which is within its original dating period. This material expires in 1999 and although it is very stable, we have no assurance that it will continue to remain stable; therefore, starting at the expiration date, we plan to continually revalidate this material. Thus, we need to know whether FDA would allow us to use the Gedeon Richter bulk drug substance as a "gold standard," if the Roussel material loses stability.

We are enclosing an analysis of the discrepancies our experts have found between the Roussel process and the Gedeon Richter process (Attachment A), as a basis for discussion of the utility of the Gedeon Richter bulk drug substance. During our meeting (Agenda Item IB), we would like to discuss the nature of these differences and what effect they may have on your allowing us to use the Gedeon Richter bulk drug substance as a "gold standard" in validating new manufacturing operations. We need to know, preferably in writing, the potential utility of the Gedeon Richter material, based on the manufacturing information obtained from Gedeon Richter and filed in Amendments No. 8 (August 5, 1997) and 9 (September 24, 1997). If additional data are needed to support use of the Gedeon Richter bulk drug substance as a "gold standard," then would the Agency be specific as to what data are needed to allow such use?

The enclosed material (Attachment A) is being provided in advance for your review. Additionally, we will make a short presentation to update you on our new manufacturer and timelines, and then wish to proceed with an open discussion of the agenda items. Please call me if you have any questions or need additional materials before the March 16th meeting.

Very truly yours,

Sandra Arnold

Attending the March 16th Meeting:

Sandra Arnold, Population Council
, NeoGen Investors, L.P.
, NeoGen Investors, L.P.

Patricia C. Vaughan, Esq. Population Council
Frederick Schmidt, Ph.D., Population Council

ATTACHMENT A:

Discrepancies-Roussel-Gedeon Richter Processes

of addition or reaction conditions. Additionally, many could add to manufacturing cost, GR's adding many physical drying steps requires added processing and solvents all adding to cost and probably productivity.

Why would GR make all these changes if they were expected to follow the R process? Either they didn't have access to the details of the R process or they carried out laboratory studies that led them to an alternate process presumably without any adverse impact on quality. These changes would normally require significant documentation to justify the changes. This documentation has not been provided to us; hence, we are unable to evaluate the impact of these changes.

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

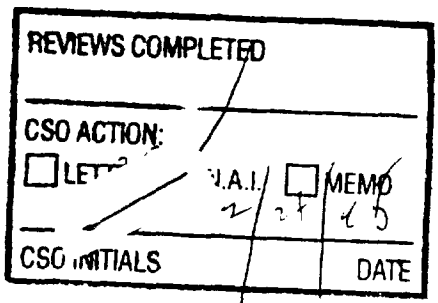
ORIGINAL

NEW CORRESP

January 30, 1998

VIA FEDERAL EXPRESS

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 012-Authorization for NeoGen to Interact with FDA on NDA

Dear

This amendment number 012 to NDA 20-687 authorizes the FDA to communicate directly with certain representatives of NeoGen investors, L.P. (NeoGen) in all matters relating to our pending NDA 20-687 (mifepristone 20 mg Oral Tablets). NeoGen is the U.S. Licensee of The Population Council for mifepristone and will be commercializing mifepristone when the NDA is approved. We believe that direct communication between NeoGen and the FDA about our pending NDA will facilitate the regulatory process. The ability of NeoGen to communicate with you is an addition to the existing communication channels between The Population Council and the FDA. Let me reassure you that NeoGen communications with the FDA will be discussed in advance with The Population Council to prevent duplication or differences.

The Population Council will continue at this time to retain the ownership of the NDA, and will be in communication with NeoGen regarding any direct discussions with the FDA. Therefore, official written notices should continue to be directed to our attention at The Population Council.

You are hereby authorized to communicate directly with the regulatory attorney for NeoGen, and his colleagues of is an attorney experienced in FDA statutes and regulations and was a . In addition, you are hereby authorized to communicate directly with who is

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

[redacted] has spent almost [redacted]

If you have any questions about this authorization, please don't hesitate to contact me to discuss them.

Very truly yours,

Sandra P. Arnold
Vice President, Corporate Affairs
The Population Council

cc: [redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	Jan. 30, 1998
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(212) 339-0663	(212) 755-6052

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

1230 York Avenue
New York, NY 10021

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20,687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
	RU 486

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 006607

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Authorization for NeoGen to Interact with FDA on NDA.

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sandra Arnold	Sandra P. Arnold, Vice President	Jan. 30, 1998

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Dag Hammarskjold Plaza, New York, NY 10017	(212) 339- 0663

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FORM FDA 356h (7/97)

MIF 006608

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

/S/ 2/23/00

/S/

NEW CORRESP

NEW CORRESP

January 30, 1998

VIA FEDERAL EXPRESS

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

not fwd /S/ 2/19/00

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE

RE: NDA 20-687, Mifepristone 200mg Oral Tablets
Amendment 011-Request for Meeting

Dear

Since our meeting with you in August 1997, we have been diligently working toward making arrangements to manufacture mifepristone. Of particular importance, we have reached an agreement with a new firm to manufacture the bulk drug substance. Given this development, we believe it is appropriate to have a meeting to update you on our progress and to solicit your advice on how best to proceed in completing the remaining requirements for approval of our NDA.

To this end, we respectfully request a meeting with you and representatives of your staff as you deem appropriate to discuss issues in accordance with the following agenda:

I. Plan for amending NDA to include new bulk drug substance manufacturer:

   A. Discussion of FDA's assessment of the CMC from Gedeon Richter and use of their pilot batches as standards,
   B. Discussion of demonstrating comparability to Gedeon Richter bulk drug substance given their differences with the Roussel process,
   C. Discussion of demonstrating comparability of the new bulk drug substance to Roussel material.

II. Discussion of the possible use of Gedeon Richter pilot batches for compassionate patient use in the United States.

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

III. Discussion of the use of [redacted] mifepristone plus higher prostaglandin dosages promoted by others versus the existing NDA dosages. What type of clinical data would be required for the Population Council/NeoGen to amend its NDA for use of these lower dosages.

We hope to schedule this meeting in late February or early March, and anticipate providing you with background material at least two weeks prior to our meeting. We will contact you early next week to discuss possible dates that you might be available.

If you have any c estions, please do not hesitate to contact me.

Very truly yours,

Sandra P. Arnold
Vice President, Corporate Affairs
The Population Council

cc: [redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	January 30, 1998
TELEPHONE NO. *(Include Area Code)* (212) 339-0663	**FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously submitted) NDA 20,687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* RU 486

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 006611

ORIGINAL
ORIG AMENDMENT

The Danco Group

Reviewed.
See Chem Rev #3
/S/
2/19/00

June 3, 1999

[redacted]

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 025- Chemistry, Manufacturing and Controls (CMC) Section for Drug Substance

Dear [redacted]

We are filing the CMC section for our Drug Substance Manufacturer.

We understand that the FDA is under no obligation to review submitted material until the complete response is received. However, as per our discussions with the FDA at the April 9 meeting and reflected in the minutes, we request that the FDA initiate review of this CMC submission as soon as possible.

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

Sincerely,

[redacted]

President and
Chief Executive Officer

/S/ 2/19/00

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 [redacted]

/dns
Enclosure

CC: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council
[redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	June 3, 1999
TELEPHONE NO. *(Include Area Code)* (212) 339-0663	**FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (Chemical Abstracts) - (11β,17β)-11-[[4-(Dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one — CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
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REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current plication)

MIF 006614

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
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	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
   Local, state and Federal environmental impact laws.

If application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmidt for	Sandra P. Arnold, Vice President	June 3, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Dag Hammarskjold Plaza, New York, NY 10017	(212) 339-0663

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (7/97)

MIF 006615

Population Council

ORIGINAL

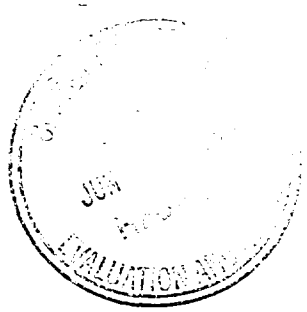
ORIG AMENDMENT

B2

Sandra P. Arnold
Vice President
Corporate Affairs

noted
6/8/99
/S/

June 3, 1999



VIA FEDERAL EXPRESS

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 200 mg Oral Tablets
Amendment 024-Final Reports for the U.S. Clinical Trials on "Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days"

Dear ———

Enclosed are the final reports of the clinical trials 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." These trials were conducted concurrently in the United States under identical protocols (166A and 166B) to evaluate the regimen of 600 mg mifepristone followed by an oral dose of 400 μg misoprostol two days later.

The results of these studies are presented in the following series of reports included in this submission:

- Study Report - Efficacy/Safety for Protocol 166A
- Study Report - Efficacy/Safety for Protocol 166B
- Study Report - Acceptability/Feasibility for Protocol 166A
- Study Report - Acceptability/Feasibility for Protocol 166B
- Combined Summary of Effectiveness for Protocols 166A and 166B
- Combined Summary of Safety for Protocols 166A and 166B
- Combined Summary of Acceptability and Feasibility for Protocols 166A and 166B

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

Draft versions of the reports for these studies were previously submitted under IND ——— Serial Number 185, on May 5, 1997.

Please contact me should there be any questions or comments regarding this submission.

Very truly yours,

Sandra Arnold

APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Continuation of Protocol 166A

Appendix C

Part B. Protocol Cover Sheet

APPEARS THIS WAY
ON ORIGINAL

Continuation of Protocol 166A

Appendix C

Part C. Protocol and Informed Consent, Protocol Amendments, Case Record Forms

APPENDIX C
THE POPULATION COUNCIL PROTOCOL 166A

B. PROTOCOL COVER SHEET

Study Phase: III

Name of Drug:
Active Ingredient: Mifepristone
Dosage: 600 mg
Route of Administration: oral
Duration of Treatment: single dose

Objective: the study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprostol in a setting within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

Patient Population: women at least 18 years of age who were ≤ 63 days from onset of their last menstrual period and who requested a voluntary termination of pregnancy.

Structure: open-label, single treatment group with patients stratified by gestational age (≤ 49, 50 - 56, 57 - 63 days).
Multicenter: yes
Number of Centers: 8
Common Training: yes
Blinding: none
Method of Patient Assignment: all patients were assigned to treatment with 600 mg mifepristone and 400 μg misoprostol.

Concurrent Control: none

Estimated Total Sample Size: 1050

Statistical Rationale Provided: no

Primary Efficacy Variable: proportion of patients with complete expulsion of the products of conception.

Adverse Reactions: observed/volunteered

Plan for Data Analysis: yes

Amendment 3
May 5, 1995

CONFIDENTIAL

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: 166A,B

SPONSOR: The Population Council, Inc.
1230 York Avenue
New York, New York 10021

_____

Signature, Principal Investigator

Protocol approved by The Population Council's IRB on September 14, 1994
Amendment No. 1 approved by The Population Council's IRB on November 2, 1994
Amendment No. 2 and 3 approved by The Population Council's IRB on May 5, 1995

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1. INTRODUCTION

Mifepristone is a synthetic steroid currently used for medical abortion in France, Sweden, United Kingdom and China. It acts as a competitive blocker of progesterone and cortisol through binding to their receptors. Because of its antiprogesterone activity, mifepristone has been developed primarily as a medical abortifacient. When used alone in different regimens with total doses ranging from 140 to 1600 mg administered over one to ten days, the success rate of abortion in women with amenorrhea of less than 50 days duration usually varied between 64-85%[1].

Subsequent studies demonstrated that when mifepristone (600 mg) was followed two days later by a prostaglandin analog administered either by the intramuscular route (sulprostone, a prostaglandin E_2 analog), or as a vaginal pessary (gemeprost, a prostaglandin E_1 analog), the efficacy rate for complete abortion increased to 95% and above. Based on these observations, mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion for the termination of pregnancies in women with amenorrhea of 49 days or less. Recently, this mifepristone - prostaglandin regimen was approved in the United Kingdom, and in Sweden. In the latter two countries, this combination is used in women with amenorrhea of up to 63 days.

In Europe there is now an accumulated experience with over 150,000 subjects who have received mifepristone together with various prostaglandins. Clinical trials have been conducted in several countries and have confirmed the initial experience. Unlike treatment with mifepristone alone where the success rate decreased with advancing duration of amenorrhea, the combination was effective up to 63 days of amenorrhea and in various published studies, the incidence of abortion induction ranged from 92.7% to 99%[1].

The most comprehensive study published to date comprises 16,369 subjects from over 450 clinics[2]. In this study 0.8% of the cases experienced uterine bleeding significant enough to necessitate vacuum aspiration or dilatation and curettage and in 0.07% (11 women), a blood transfusion was required. Significant cardiovascular side effects were reported in four cases following sulprostone administration. In three of these subjects, there was severe hypotension necessitating infusion of macromolecular solutes and in the final subject, a 38 year-old smoker, there was an acute myocardial infarction. In these four subjects, symptoms commenced within one hour of sulprostone administration and all recovered uneventfully. However, in general use, there was a fatal myocardial infarction in one woman, who was a 31-year-old heavy smoker, following sulprostone[3]. No cardiovascular complications have been reported following gemeprost, but this may be related to the fact that this analog has been used less often than sulprostone. Sulprostone is rapidly absorbed into the circulation following intramuscular injection.

therefore, it is not unreasonable to assume that this prostaglandin carries a higher risk of cardiovascular problems than preparations that are administered orally or vaginally and are absorbed more gradually. Moreover, gemeprost, unlike sulprostone, is an E_1 analog.

As a consequence, parenteral prostaglandins should be used cautiously in women with heart disease, those over 35 years of age or in heavy smokers. The French health authorities have in fact withdrawn sulprostone as one of the prostaglandin preparations which can be given with mifepristone.

Because of the cardiovascular side effects reported with sulprostone as well as the inconvenience of both sulprostone and gemeprost which both require refrigeration, alternate prostaglandin preparations are now being used. Misoprostol, (methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13 E-en-1-oate) is a prostaglandin E_1 analog that has been safely used for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk for complications from gastric ulcers for many years; for this indication, it is given in an oral dose of 200 μg four times daily. Its effects on uterine tone are similar to those of other prostaglandins. Misoprostol is inexpensive, orally active and stable. In a recently published French study in women with amenorrhea of 49 days or less, one group comprising 505 women received 400 μg misoprostol 48 hours after mifepristone; the success rate for termination of pregnancy was 96.9%[4]. A second group of 390 women initially followed the same protocol. In this second group, the overall success rate was 98.7%. These results indicate that the combination of mifepristone and misoprostol is of equal or greater effectiveness than the combination of mifepristone and either parenteral or vaginal prostaglandin for the termination of early pregnancy.[4] No serious cardiovascular side effects have been observed. Other side effects were neither more frequent nor more severe than after either parenteral or vaginal prostaglandin preparations[4].

A study from Britain reported complete abortion in 92 out of 99 women with amenorrhea of less than 57 days who were given 200 mg mifepristone followed 48 hours later by 600 μg misoprostol. There were three on-going pregnancies and four incomplete abortions. Vomiting was exhibited in 24% and diarrhea in 7% of the women. No analgesia was needed in 62% of the women[5].

In the two studies reported above, approximately 60-80% of women aborted during the four hours following prostaglandin administration. A number of side effects have been observed during this four hour period. These include: uterine pain, nausea, vomiting and diarrhea. In one of these studies the incidence of nausea, vomiting and diarrhea were 43%, 17% and 14% respectively[4].

In Europe, over 52,000 women have received mifepristone followed 48 hours later by misoprostol without serious heart complications.

2. SUMMARY OF STUDY

The aim of the study is to determine the safety, efficacy, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion, within the U.S. health care system setting, when administered to women exhibiting amenorrhea of varying duration (up to 63 days). The duration of amenorrhea will be defined throughout this document as the number of days from the first day of the last menstrual period. In addition to the large pivotal studies, a small initial pilot study will be conducted to enable the investigators to gain first hand experience with the proposed dosing regimen.

A total of 1,050 pregnant subjects will be enrolled in this and an identical sister protocol, to be conducted simultaneously. Thus a total of 2,100 subjects will be enrolled in the two trials. Three groups of subjects will be examined:

Group 1: Amenorrhea of $\leq$ 49 days
Group 2: Amenorrhea of 50 through 56 days
Group 3: Amenorrhea of 57 through 63 days

Analysis will also be conducted on safety, efficacy and acceptability of all subjects taken as a single group, regardless of the duration of amenorrhea. This will be a multicenter trial utilizing a minimum of six centers in each of the two studies. The centers will all perform pregnancy interruption on a regular basis. The centers will have access to facilities for blood transfusion and routine emergency resuscitation techniques. In all the trial centers, the recruitment of subjects will be such that, as closely as possible, equal numbers of subjects will be enrolled into each of the three groups defined above.

Subjects shall visit the study center three times, unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin. At the initial visit (Day 1; after any required statutory waiting period), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study

will return to the center two weeks post the surgical procedure for a follow-up assessment.

3. OBJECTIVE

The objective of this trial is to evaluate the effectiveness, safety, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion when given to women, who have experienced up to 63 days of amenorrhea, within the U.S. health care system setting. Prior to initiation of the pivotal studies, a pilot study comprising 15 women will be performed at each of the selected study centers. The purpose of this pilot trial is to give the investigators exposure to the proposed dosing regimen so they will have first hand experience prior to the initiation of the pivotal studies. The results of the pilot trial will be included in the safety analysis for the product, but the efficacy data will be treated as a subgroup analysis relative to the pivotal trials.

Investigators selected to conduct the trials will be experienced abortion providers and medical investigators. They should have access to an IRB able to review the protocol, and will have malpractice insurance as well as general liability insurance for the clinic, hospital or office where the study will be performed. The investigators should be able to complete the study in six months at a maximum.

The investigators will operate in an appropriate study center; the study center will:

a) Provide routine emergency resuscitation such as O_2, Ambu bag and will be staffed with personnel trained in routine emergency care.

b) Have access on a 24 hour a day basis to blood transfusion, D & C and more elaborate resuscitation procedures.

c) Have space to conduct the study including a room where a woman can be monitored for at least four hours after the prostaglandin administration.

d) Have the physician responsible for the study on call on a 24 hour a day basis, or his/her delegate of equal qualification.

e) Have adequate and sufficient trained personnel for counselling of subjects and conduct of the study.

f) Have transvaginal ultrasound available and personnel trained in the use of the equipment as well as the interpretation of the sonograms for the assessment of gestational age in relation to the reported duration of amenorrhea.

g) Investigators and staff will answer a provided questionnaire at the completion of the study.

4. PATIENT SELECTION

4.1 Patient Sample:

4.1.1 Number of patients: A total of 1,050 patients per each of the identical trials for a total of 2,100 subjects will be enrolled at multiple centers.

4.1.2 Age range: 18 years or older.

4.1.3 Residents of the United States.

4.2 Inclusion Criteria:

4.2.1 Good general health.

4.2.2 Age 18 years or older.

4.2.3 Request termination of pregnancy.

4.2.4 Agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated.

4.2.5 Have an intrauterine pregnancy of known duration which is less than or equal to 63 days of amenorrhea period. The final determined estimated duration of pregnancy should be less than 64 days of amenorrhea, and as confirmed by uterine size on pelvic examination and ultrasonographic examination.

4.2.6 Have a positive urine pregnancy test.

4.2.7 Willing and able to participate in the study after its precise nature and duration have been explained.

4.2.8 Able and willing to sign an informed consent form.

4.2.9 Resident of the United States.

4.3 Exclusion Criteria:

4.3.1 Evidence of the presence of any disorder which represents a contraindication to the use of mifepristone (e.g., chronic corticosteroid administration, adrenal disease) or misoprostol (e.g., asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or known allergy to prostaglandin).

4.3.2 History of severe liver, respiratory, or renal disease or thromboembolism.

4.3.3 Cardiovascular disease (e.g., angina, valve disease, arrythmia, cardiac failure).

4.3.4 Hypertension being treated on a chronic basis or untreated patients who present with: a blood pressure of > 140 (systolic) or > 90 (diastolic).

4.3.5 Anemia (hemoglobin level below 10 g/dL or hematocrit below 30%) at the Day 1 visit.

4.3.6 A known clotting defect or receiving anticoagulants.

4.3.7 Subjects with an IUD in place.

4.3.8 Insulin dependent diabetes mellitus.

4.3.9 More than 63 days of amenorrhea or results of bimanual pelvic examination or vaginal ultrasound which are inconsistent with 63 days or less of amenorrhea.

4.3.10 Breast-feeding.

4.3.11 Adnexal masses or adnexal tenderness on pelvic examination suggesting pelvic inflammatory disease.

4.3.12 Ectopic pregnancy or threatened abortion.

4.3.13 Women 35 years of age or older who smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g., diabetes mellitus, hyperlipidemia, hypertension or family history of ischemic heart diseases).

4.3.14 Unlikely to understand or comply with the protocol requirements.

4.3.15 Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place of work and (b) the abortion center.

5. STUDY MEDICATION

5.1 Assignment of Study Medication

This is a multicenter trial evaluating the effectiveness, safety and acceptability of mifepristone plus misoprostol in inducing abortion when given to women in one of three groups depending upon the duration of amenorrhea. The three groups are:

Group 1 - Amenorrhea of $\leq$ 49 days
Group 2 - Amenorrhea of 50 through 56 days
Group 3 - Amenorrhea of 57 through 63 days

As closely as is possible, equal numbers of subjects will be enrolled into each of the three groups. There may be differing numbers of patients enrolled from center to center, but the number per group per center should be approximately one third into each of the groups.

5.2 Dosage and Administration

There will be three visits to the study center. At the initial visit (Day 1), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered orally. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed and an acceptability questionnaire administered. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

5.3 Packaging

A) Mifepristone — Mifepristone will be provided as 200 mg tablets of micronized mifepristone.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol.

All study supplies will be kept in a locked, dry cabinet.

5.4 Labeling

A) Mifepristone — Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol and dispensed from the center pharmacy.

5.5 Concomitant Medications

No salicylates, indomethacin, or any other drug which inhibits prostaglandin synthesis should be taken. If necessary, analgesics belonging to other pharmacologic classes or spasmolytic drugs may be used. Drugs such as trifluoperazine and related phenothiazines (for treatment of nausea and vomiting) that could increase the risk of hypotension must be avoided as should oxytocin and any other prostaglandin preparation.

The use of concomitant medications during the course of this study will be recorded in the Case Report Form, and these data will be analyzed.

6. STUDY PROCEDURES

Each participating study center will record on a daily basis the number of subjects recruited in each of the three groups. All women approached to participate in the study will be recorded in the study data. Those who refuse to participate in the trial will have a special form completed for the database. These data will be communicated to the sponsor on a weekly basis. At each center, the number of subjects recruited into each of the groups will be equal to one-third the total assigned to the center if possible. When any of the groups has been filled, no further recruitment into that particular group will be conducted. Under no circumstances will any member of the study center staff suggest that a subject appearing at the center, with a duration of amenorrhea consistent with a completed group, be deferred in her request for pregnancy termination to allow for enrollment into an open group at a later time.

6.1 VISIT 1 (Admission, Day 1 of Study)

At the time of the subjects enrollment (Day 1), all the following should be done:

- Counseling.

- Medical, obstetrical and gynecological history.

- Medical examination, including: height, weight, blood pressure, and pulse.

- Bimanual pelvic examination.

- Urine pregnancy test.

- Quantitative Serum ßhCG.

- Vaginal ultrasound.

- Determination of Rh status and where routinely collected, the blood group.

- Hemoglobin or hematocrit determination.

Blood samples will also be collected prior to the administration of mifepristone for the following:

Chemistry Panel (4mL)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3mL)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count*

Food should be withheld for one hour prior to and one hour post administration of the study drug. At admission to the study, the three tablets of mifepristone (600 mg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.

Subjects who smoke will be instructed to refrain from smoking until after the administration of misoprostol at Visit 2, and an appointment will be made for Visit 2.

Subjects will be given a copy of the informed consent and patient diary card describing symptoms which require emergency treatment. These include: heavy bleeding, fever, and severe abdominal pain. The subjects will be given the address and 24 hour telephone number of a medical center (including the name of physicians) which cares for patients on a 24 hour a day basis.

A diary will be provided to each of the subjects for recording medications and symptoms, such as pain, nausea, vomiting and diarrhea. The diary will also be used to record the occurrence of vaginal bleeding on each day. The subject will be instructed to record the bleeding relative to their normal menstrual flow (e.g., lighter, the same as or heavier than normal). If the expulsion takes place before Visit 2, the date and time should be recorded on the subjects diary.

* Amendment 2 dated April 27, 1995

6.2 VISIT 2 (Prostaglandin Administration, Day 3 of Study)

Visit 2 will be conducted on Day three (3) of the study. The following will be performed:

- Clinical examination.

- If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.

- Brief interview and review of the diary.

- Any adverse events which occurred since Visit 1 will be recorded on the case report form.

- Subject will receive an injection of anti-D globulin if the subject is Rh negative, if indicated.

- Food should be withheld for one hour prior to and one hour post the administration of misoprostol. The two tablets of misoprostol (400 μg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.
- The subject will be observed at the study center for the four hour period post the administration of misoprostol at a minimum. The facility should be capable of surgical termination of pregnancy (by vacuum aspiration or dilation and curettage) and have access to blood transfusion and emergency resuscitation.

- During the observation period, the following should be recorded at least hourly:

- Occurrence of nausea, vomiting, or diarrhea. Intensity should be recorded as:

0: none
1: mild
2: moderate
3: severe

Any treatment for these will be recorded as concomitant medications.

- At the onset of any abdominal pain, the following will be recorded:

Intensity, recorded as: none, mild, moderate, or severe.

Duration, documenting any treatment as a concomitant medication.

- Blood pressure and heart rate at hourly intervals unless more frequent readings are indicated.

- Time of expulsion, if occurring during the observation period.

- Any unexpected symptom or clinical finding.

The use of intramuscular sulprostone in combination with mifepristone in previous studies has occasionally precipitated an episode of hypotension usually associated with bradycardia. In extremely rare circumstances this previously utilized treatment regimen has been associated with myocardial infarction and ventricular tachycardia. These complications are very unlikely with the combination of misoprostol and mifepristone. However, any significant fall in blood pressure or significant change in heart rate, however transient, following the administration of misoprostol will be recorded and the subject observed for at least three hours after their blood pressure and heart rate have returned to baseline. In case of chest pain, hypotension or cardiac arrhythmia, an ECG should be performed immediately and if required adequate resuscitation should be undertaken.

The cycle immediately following the administration of mifepristone is ovulatory. Therefore, subjects will be counseled to initiate contraception. Barrier contraception may be initiated within three days of misoprostol administration.

- A gynecological examination will be performed to determine if products of conception remain in the vagina or cervix.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.3 VISIT 3 (Exit Interview, Day 15 of Study)

Visit 3 will be conducted on Day fifteen (15) of the study. At Visit 3 the following will be performed:

- Clinical and gynecological examination.

- Assessment of severity and duration of uterine bleeding. Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.

- Assessment of hemoglobin or hematocrit if indicated.

- Blood samples will be collected for:

Chemistry Panel (4mL)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3mL)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count

A total of twelve (12) subjects per each group of amenorrhea duration, for a total of thirty-six (36) per center will be involved in these assessments at six (6) selected centers. Thus, a total of 216 subjects from the entire study population will participate.*

- Verification of any concomitant medications or other therapeutic measures since Visit 2.

*Amendment 2 dated April 27, 1995

- Assessment of expulsion (history, pelvic examination), as well as date and time of occurrence if appropriate.

- Final evaluation of the treatment outcome through the clinical and gynecological examination. If necessary, perform ultrasonography and/or urine pregnancy test.

- In instances where the medical abortion method has failed, either completely or partially, perform the necessary additional surgical procedure. In the subjects for whom a surgical procedure is required, schedule a follow-up visit as per Section 6.6 below.

- Examine the subject's view of her abortion experience including her view of the experience relative to expectations; assessment of discomforts and side effects; timing and place of abortion; satisfaction with the experience; comparison to any previous abortion experience; best and worst features of the method being assessed in the trial; attitude toward self-administration of prostaglandin at home and preference for home or clinic treatment. All responses will be recorded in the case report forms.

- Assure that the subject's case record forms have been completely, accurately and properly filled in.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 3 appointment.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.4 UNSCHEDULED VISITS

At Visits 1 and 2, subjects will be advised that they may return to the study center at any time if they experience medical problems associated with the medical abortion or for any other medical problem. At any unscheduled visits the following will be recorded:

- Reason for the visit.

- Use of any concomitant medications since the last visit.

- Information regarding utilization of any other medical resources.

- Pregnancy status at onset of visit.

- Temperature, blood pressure, heart rate, and hemoglobin.

- Any medication administered during visit as well as any medications prescribed.

- Any procedures conducted during the visit.

- Results of any pathology testing.

Subjects who have a surgical abortion at any unscheduled visit will have the exit interview (As defined in Section 6.3 above) prior to departure from the study center on the day of the surgical abortion, and will not return for the scheduled Visit 3. However, subjects undergoing surgical abortion will be scheduled for a follow-up visit as outlined in Section 6.6 below.

6.5 MEDICAL ADVISORY COMMITTEE

If serious adverse events occur beyond expectation, the decision of whether or not the study should be discontinued or modified will be taken by the Sponsor in consultation with the Medical Advisory Committee.

6.6 FOLLOW-UP

Subjects who are enrolled and receive either or both drugs in the study and undergo surgical abortion at any time during their enrollment will be scheduled for a follow-up visit. This follow-up visit will be scheduled for two weeks post the date of the surgical abortion. At this visit the following will be recorded:

- Brief medical history and clinical examination.

6.7 EARLY WITHDRAWAL FROM THE TRIAL

Subjects may withdraw from the study at any time at their own request. In all cases, the reasons for the subjects withdrawal must be recorded in detail in the case report forms and in the patients medical records. In all cases of withdrawal the subjects must be encouraged to have surgical abortions. If any subject refuses surgical abortion, the investigator must record that the subject understands the

risks involved in allowing the pregnancy to continue once drug treatment has begun. **A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**

All efforts will be made to contact subjects who fail to return for the necessary visits (telephone, registered mail). The subject will not be given misoprostol if contacted after 60 hours of the study. A subject may not complete the treatment regimen if severe side effects or symptoms develop after mifepristone administration that, in the opinion of the principal investigator, constitute a threat to the woman's health. Any subjects who do not complete the treatment regimen for any reason will be assessed for the completeness of the abortion, if possible. Any subject who has received mifepristone and has at the time of early termination had an incomplete abortion, as described above, will undergo surgical abortion as described in Section 6.3 above, and will be considered a failure.

7. ADVERSE EXPERIENCES

7.1 General Aspects

Adverse Reactions

Subjects will be notified of possible adverse reactions; they will be instructed to immediately report all adverse reactions to the investigator.

Any adverse reaction, noticed by the investigator or reported by the subject, including clinically significant lab abnormalities, will be recorded in the appropriate section of the case report form, regardless of its severity and relationship to study drug.

Serious or unexpected adverse events will be immediately reported by the investigator by telephone to:

Dr. Irving Spitz
Dr. C. Wayne Bardin
The Population Council, Inc.
(800) 327-8730
24 hour answering service outside normal business hours

—— will notify the sponsor, and ensure FDA notification. All serious ("any experience that is fatal or life-threatening, is permanently disabling, incapacitating, requires inpatient hospitalization, or causes a congenital anomaly, cancer or is due to overdose") and/or unexpected ("any adverse experience that is not identified in nature, severity or frequency in the current investigator's brochure for the study") adverse

reactions must be immediately (within 24 hours) reported by telephone to the Sponsor and a written report must be submitted to the medical monitor within 24 hours.

The initial telephone contact will be followed within 3 days by a detailed report of the event which will include copies of hospital case reports, autopsy reports and other documents, when applicable. The adverse event must be followed through resolution.

The same applies to all subjects who died during the course of the study or within 30 days of completion of treatment irrespective of whether the adverse reaction was judged as related to treatment. In case of a death, copy of the autopsy report should be sent to the sponsor, if performed.

For each adverse reaction, the following information will be entered in the case report form: description of event, onset date, resolution date, severity (1=mild, awareness of sign or symptom, but easily tolerated; 2=moderate, discomfort enough to cause interference with usual activity; 3=severe, incapacitating with inability to do usual activity), drug cause-effect relationship and the outcome of the event. The investigator will also note if any action was taken regarding the test drug (temporarily or permanently discontinued) and if therapy or hospitalization was required.

ETHICAL ASPECTS

A. Informed Consent Form

The purpose of the study, those adverse reactions that are known to occur with the study drugs and the subject's right to withdraw from the study at any time without prejudice, must be explained to each subject in a language she understands. The subject is then required to sign in the presence of a witness an approved informed consent form in a language she understands containing all the above-mentioned information and a statement that the subject will permit examination of his/her study case report forms by a third party. Willing subjects may be interviewed by a representative of the sponsor about her understanding of the risks, benefits, procedures, and the experimental nature of the study.

B. Institutional Review Board

This study will not be initiated until the protocol and informed consent form have been reviewed and approved by a duly constituted Institutional Review Board (IRB) as required by U.S. FDA regulations. It is the responsibility of the investigator to submit the study protocol with its attachments to the IRB for review and approval.

The names and professional affiliations of all the members of the board or the IRB general assurance number must be given to the Sponsor of the study prior to study initiation, along with a signed and dated statement that the protocol and informed consent form have been reviewed and approved by the IRB.

The investigator is committed, in compliance with FDA regulations, to inform the IRB of any emergent problems, serious adverse reactions or protocol amendments.

C. Protocol Amendments

Any amendment to the protocol will be with mutual agreement between the investigator and the Sponsor. All amendments to the protocol will be submitted to the FDA and to the Institutional Review Board (IRB) concerned for review and, if necessary, approval prior to implementation of the changes.

D. Study Monitoring

A pre-study visit will be made by the monitor to the investigative site in order to review the protocol and to ascertain that the facility is adequate for satisfactory conduct of the study, as well as to discuss the obligations of both the sponsor and the investigator.

The investigator will permit a representative of the sponsor or his designate and the FDA, if requested, to inspect all case report forms and corresponding portion of the study subjects original office and/or hospital medical records, at regular intervals throughout the study. These inspections are for the purpose of assessing the progress of the study, verifying adherence to the protocol, determining the completeness and exactness of the data being entered on the case report forms and assessing the status of study drug storage and accountability. During site visits, case report forms will be examined by the study monitor(s) and verified by comparison with corresponding source data (such as hospital and/or office records).

ADMINISTRATIVE ASPECTS

A. Curricula Vitae

The investigator will provide the Sponsor with copies of the curricula vitae of himself/herself and the co-investigators listed on the FDA Form 1572.

B. Data Collection in the Case Report Form

A Case Report Form in triplicate will be provided by the sponsor for each subject to be filled in at each visit. Additional forms will be used for screening of the subjects prior to enrollment. In the event of additional visits, extra case report forms for the unscheduled visits will be filled out. At the visits on Days 1 and 15, acceptability questions will be asked, and the data recorded.

Acceptability questions will be asked on the day of surgical abortion for those having a surgical abortion.

One copy of the forms will be retained by the clinical study site, the other copies will be retrieved by the study monitor at the monitoring visits. All forms will be filled in legibly in black ball point pen. All entries, corrections and alterations are to be initialed and dated by the investigator, co-investigator, or study coordinator making the correction. Corrections will be made by crossing through the incorrect data with a single line so that the incorrect information remains visible, and putting the correct information next to the incorrect data. A reasonable explanation must be given by the investigator for all missing data.

C. Data Retrieval

At intervals during the study and at the conclusion of the study, the study monitor will retrieve signed and dated case report forms from the study site for data entry and analysis. The original and one copy of each page will be retrieved by the monitor. The investigator will keep a copy of all original case report forms and source documents.

D. Records Retention

Except as otherwise explicitly set forth herein, pursuant to applicable federal regulations, the investigator must retain copies of all study records for a period of two (2) years following the date a marketing application is approved for the indication for which the drug is being investigated. If no application is filed or if the application is not approved, the study records must be retained until 2 years after the investigation is discontinued and FDA is notified.

E. Study Termination

Either the investigator or the sponsor may terminate the study at any time for well documented reasons, provided a written notice is submitted at a reasonable time in advance of intended termination.

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8. STATISTICAL ANALYSIS

8.1 Population Analyzed

All subjects to whom mifepristone has been administered will be included in the analyses.

A) Efficacy

Efficacy will be determined by each subject's abortion status and history at Visit 3 (Day 15), two weeks post the administration of mifepristone. The pregnancy/abortion status requires a clinical evaluation, including where necessary ultrasonographic and/or urine pregnancy results.

One measure of success will be defined as a pregnancy termination by Visit 3 (Day 15) without the need for surgical or instrumentation procedures except for forceps extraction of ovular tissue fragments extending through the external cervical os. If pregnancy has not been terminated by Visit 3 (Day 15), this will be considered a failure.

FAILURES

Two categories of failures will be recognized. These will be called medical failures and acceptability failures.

Medical failures are of two types:

i) persisting pregnancy at Visit 3 (Day 15).
ii) medically indicated surgical intervention because of:
    a) incomplete expulsion at Visit 3 (Day 15).
    b) serious adverse advents that warrant early surgical interruption of pregnancy.

Acceptability failures are deemed to have occurred when subjects request surgical interruption of a persisting pregnancy before Visit 3 (Day 15) without medical necessity.

In consequences of this distinction between types of failure, there will be two evaluations of success and failure rates.

The *medical failure rate* (MFR) will be determined by life table analysis on a day to day basis from Visit 1 (Day 1) through Visit 3 (Day 15). Women who request surgical abortions before Visit 3 (acceptability failures) will be considered as censored as of mid-day on the day of the surgical abortion. Persisting pregnancies as of Visit 3 are considered failures. The method success rate is 1-MFR for any day or cumulative analysis. Women with persisting pregnancies of less than two weeks post the administration of mifepristone when last observed (e.g., lost to follow-up) will be treated as censored in mid-day of the last observation in the calculation of gross rates.

The *total failure rate* (TFR) will also be determined by life table techniques using the assumption that some of the subjects with persisting pregnancies are last observed before two weeks post the administration of mifepristone. Daily total failure rates are computed under the assumption that subjects with continuing pregnancies last observed before Visit 3 were last observed in the middle of the day of last observation.

Data will be recorded in the case report forms to allow for the distinction between medical and acceptability failures.

All failures will undergo vacuum aspiration or dilation and curettage. Material will be submitted for pathological examination.

B) Safety

Safety will be assessed utilizing the following parameters:

- Duration and severity of uterine bleeding; data obtained from subject diary, determination of hemoglobin, by treatment (e.g., transfusion, surgical procedure) necessary secondary to heavy and prolonged uterine bleeding.

- Occurrence of any adverse event or abnormal clinical finding (e.g., signs of pelvic infection).

- Adverse events linked to drug administration and abortion (e.g., nausea, vomiting, diarrhea, painful uterine contractions).

- Assessment of heart rate and blood pressure during the observation period following the administration of misoprostol.

Safety data will include all safety parameters at all visits both scheduled and unscheduled, as well as data collected in the subject's diary, of all subjects to whom mifepristone has been administered.

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C) Acceptability

Acceptability will be measured by patient interviews at the final discharge visit. The assessments will be made on the basis of answers to questions concerning:

- satisfaction with the information and counseling,
- satisfaction with the procedure,
- comparison to previous abortion experience, where applicable,
- willingness to choose the method again, and,
- willingness to recommend the method to others.

All these variables will be assessed in light of the level of complications, discomforts, and side effects recorded for each patient on both the questionnaire and symptomatology diary.

Acceptability of the regimen will also be determined through a questionnaire for providers.

D) Feasibility of Use in the U.S. Health Care System

Variability is built into the study with regard to: Type of abortion site (hospital clinic, Planned Parenthood clinic, feminist health clinic, private practice, free-standing abortion clinic), ethnicity of patient, socioeconomic status (Medicare, self-pay, insurance, help fund, etc.), and location in inner city, small city, suburb, or rural area. The association of these factors with:

- adherence to the protocol
- complications and side effects
- failure (and type of failure)
- patient satisfaction with medical abortion
- provider comfort with medical abortion

will be analyzed.

8.2 ANALYTIC METHODS

8.2.0. A detailed plan, outlining in advance the statistical evaluation of each baseline, safety and efficacy variable, will be submitted to file prior to statistical examination of the data. Essential features of this plan, as presently anticipated, are described below.

8.2.1. Descriptive Statistics: Characteristics of subjects measured at admission through the administration of mifepristone will be summarized. All variables pertaining to safety, efficacy and acceptability will be summarized.

8.2.2. Lifetable Analysis of Efficacy: Single and multiple decrement failure rates for each type of failure and for the total failure rate will be analyzed for each amenorrhea duration, and all durations. Failure rates, by duration of amenorrhea, for age, ethnic group, payment status, and service delivery groups will be determined.

8.2.3. Efficacy Analysis: Multinomial logistic models will be employed to evaluate efficacy. Successful abortion, incomplete expulsion, early surgical interruption due to medical necessity and early surgical interruption at the patient's request (no medical necessity) will serve as the outcome categories used to form response vectors for the models. In one model, the response vector will be comprised of the cumulative log odds over the three types of failure (i.e., incomplete expulsion, medical interruption and requested interruption). In another model, the response vector will be the log odds of these individual types of failure *per se*. In all models, the independent vector will be amenorrhea duration ($\leq$ 49 days, 50-56 days and 57-63 days).

The models will be used to test the overall (omnibus) effect of amenorrhea status. Additionally, pairwise contrasts among the amenorrhea groups will be evaluated. Both the overall effect and pairwise effects will be examined using traditional hypothesis tests to assess the *complete response vector* (i.e. all failure categories considered simultaneously). However, *individual response categories* will be examined in two ways. First, a traditional hypothesis test will be used to conduct a test of the overall affect of amenorrhea. Second, the examination of pairwise amenorrhea group contrasts will take the form of an equivalency test.

All traditional tests will be evaluated using a type I error rate of 0.05. Equivalence tests will be performed using 90% confidence intervals (which mathematically correspond to a type I error rate of 0.05) and an equivalence interval of $\pm$ 5 percentage points.

Single and or multiple decrement life table techniques, as appropriate, will be used to display failure rate probabilities by time, for individual amenorrhea group and all groups combined. The various effects examined using the multinomial logistic models will also be exhibited in tables and/or figures.

8.2.4. Analysis of factors associated with early abortion (Days 1-3) or late abortion (Days 4-15) or Failure will be undertaken by a variety of multivariate techniques. This analysis pertains to aspects of efficacy, safety and acceptability.

8.2.5. Baseline/Safety Analysis. Qualitative baseline and safety variables will be systematically summarized in appropriate patient groupings for examination by the medical reviewer. Descriptive statistics for baseline and safety variables that are suitable for quantitative analysis will be displayed in tables and figures. Furthermore, these variable will be evaluated across amenorrhea groups using linear models, applied to continuous or categorical variables. Continuous variables expected to markedly deviate from normality will be rank transformed to obtain nonparametric tests of significance. Any baseline variable found to exhibit a meaningful difference across amenorrhea groups, will be considered for use as covariate or blocking factor in the efficacy analysis. As a conservative measure to increase statistical power, variables exhibiting p-values of 0.20 or less will be singled out to assess their potential relevance to the safety and efficacy of the study drug.

Analysis of variables associated with need for transfusion and with severe cardiovascular adverse events will be undertaken.

8.2.6. Acceptability Analysis: Analysis of variables associated with acceptability within each duration of amenorrhea and overall shall be undertaken using both univariate and multivariate techniques.

9. RISK-BENEFIT ASSESSMENT

Experience gained to date with the use of mifepristone and prostaglandin for the termination of early pregnancy indicates that this has few side effects and a frequency of short-term complications that is comparable to that observed after vacuum aspiration. The most common complaints during treatment, particularly following administration of the prostaglandin, are lower abdominal pain, nausea, vomiting and diarrhea. In addition, bleeding for several days is common. For these complaints, appropriate medication can be prescribed when required. Occasionally, heavy uterine bleeding may necessitate emergency curettage and, very rarely, blood transfusion.

The approximate failure rate, according to the experience gained from women who have had this treatment in Europe, up to 49 days is 5%. Therefore approximately 5% of the subjects in this trial treated up to 49 days of amenorrhea will be expected to undergo surgical termination of pregnancy. It is possible the failure rate will be higher in the older pregnancies. **Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women with amenorrhea of no more than 49 days before administration of mifepristone.**

There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. This excess bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.**

Following a treatment regimen involving the intramuscular injection of the prostaglandin analog sulprostone, in a very low percentage of cases (one in 20,000), serious cardiovascular complications have been observed, including one case of fatal myocardial infarction. These complications have been most often associated with subjects who were heavy smokers, and still these complications are extremely rare. There is no evidence that misoprostol, a different class of prostaglandin, which is widely prescribed for longterm use in the prevention and treatment of peptic ulcer disease, is associated with any such cardiovascular side effects.

All subjects will be informed as to the potential complications. Centers participating in the trial will ensure that qualified personnel and necessary equipment and supplies are available at all time to deal with any complications.

Studies conducted in mice and rats have shown that mifepristone does not have any teratogenic effects. There are insufficient data to evaluate the effects of mifepristone on the human fetus. In one subject in France who took mifepristone and failed to abort, pregnancy was terminated at 18 weeks because of fetal abnormalities. The precise relationship to mifepristone could not be established[6]. Thus, in the event of a continuing pregnancy, surgical abortion should be performed. Misoprostol has been reported to be teratogenic and is reported to be associated with malformations of the scalp, cranium and other abnormalities[7].

The benefits of this form of medical termination of pregnancy are that most women participating in the study can be expected to have a complete abortion and will not be exposed to the risks associated with surgical abortion, particularly the risks of physical trauma (e.g., cervical laceration, uterine perforation, etc). Nor does medical abortion carry any anesthetic-related risk.

No financial renumeration will be offered to potential study participants.

**Amendment 3 dated May 2, 1995

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

_____ ___/___/___

Signature of Investigator M D Y

_____ ___/___/___

Signature of Sponsor M D Y

APPEARS THIS WAY
ON ORIGINAL

Table 1

	Visit 1	Visit 2	Visit 3
Counseling	X		
Medical, OB-GYN History	X		
Medical Examination	X	X	X
Pelvic Examination	X	X	X
Urine Pregnancy Test	X		X*
Quant. Serum ßhCG	X		X*
Vaginal Ultrasound	X	X*	X*
Blood Typing including Rh	X		
Hemoglobin or Hematocrit Determination	X		X*
Administration of Mifepristone	X		
Administration of anti-D globulin		X*	
Administration of Misoprostol		X	
Interview and Review of Diary		X	X

* - To be conducted if indicated

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APPENDIX 1

PROTOTYPE INFORMED CONSENT

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 B

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.**

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**

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.

APPEARS THIS WAY
ON ORIGINAL

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**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 B

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*** . 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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* 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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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**** . 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.*** 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

** Amendment 3 dated May 2, 1995

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

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 B

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**** 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.

[ ]

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 B

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).

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. _____ (telephone:_____).

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 B

APPEARS THIS WAY
ON ORIGINAL

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 (institute, address, telephone no.) In addition, I will contact Dr. _____

(telephone:_____). If he or she cannot be reached in a medical emergency related to the study, I may contact Dr. _____ (telephone:_____).

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. _____(telephone:_ _____ or Dr. _____ (telephone:_____ 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 I refuse surgical abortion and continue with my pregnancy, I risk, and the infant may risk, complications, including fetal or infant malformation.

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.

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

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 B

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

APPEARS THIS WAY
ON ORIGINAL

AMENDMENT #1

Protocol:

Cover Sheet:	Change:	The Population Council to The Population Council, Inc.
	Change:	Written authorization from The Population Council, to written authorization of The Population Council
Table of Contents: 6.5:	Change:	~~[illegible]~~ to MEDICAL ADVISORY COMMITTEE
P. 3: First paragraph:	The word either was added in reference to parenteral or vaginal prostaglandins in combination with mifepristone	
P. 3: Last paragraph:	Change:	heart condition to heart complications
P. 4: Third paragraph:	Change:	as close as possible to as **closely** as possible
P. 4: Last paragraph:	Add:	Subject shall visit the study center three times **unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin.**
	Add:	At the initial visit (Day 1); **after any required statutory waiting period.**
P. 5: second paragraph:	Change:	institutional insurance to general liability insurance
P. 6:	Add: 4.1.3	**Residents of the United States**
P. 6:	Add: 4.2.9	**Resident of the United States**
P. 7: 4.3.2	delete	~~[illegible]~~
P. 7: 4.3.5	Add:	**or hematocrit below 30%**
P. 7: 4.3.7	Delete	~~[illegible]~~
	Add:	**Subjects with an IUD in place.**
P. 7: 4.3.15	Change to:	Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place or work and (b) the abortion center.

P. 8: Section 5.2:		Clarification that 600 mg of mifepristone will be administered orally.	
P. 9: Section 5.3:	A)	Change to:	Mifepristone will be provided as 200 mg tablets of micronized mifepristone
	B)	Change to:	Misoprostol will be obtained locally be each investigator as 200 µg tablets of commercially available misoprostol.
P. 9: Section 5.4:	A)	Change to:	Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.
	B)	Change to:	Misoprostol will be obtained locally by each investigator as 200 µg tablets of commercially available misoprostol and dispensed from the center pharmacy.
P. 9: Section 5.5 paragraph 1		Change: ——— to hypotension Change: should be avoided to **must** be avoided	
P. 10: Section 6.1:		Change:	Serum βhCG test to quantitative serum βhCG.
		Change:	Determination of blood group and Rh status to Determination of Ph status and where routinely collected, the blood group.
P. 10: Last paragraph:		Add:	**No more than** 240 ml.
P. 11: Second paragraph:		Change:	Subjects will be given written information **to** Subjects will be given a copy of the informed consent and patient diary card.
		Change:	.... which receives patients ..... **to which cares** for patients.
Section 6.2:		Add:	**If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally**

			that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.
	Last paragraph:	Delete:	~~_____~~
		Add:	**, if indicated.**
P. 12:	First paragraph:	Add:	**No more than** 240 ml
	Second paragraph: Last sentence	Delete:	~~_____~~
P. 13:	Section 6.2: Second to Last paragraph	9/6/94 last paragraph Change to:	A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.
P. 13:	Section 6.2:	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 13:	Section 6.3:	Add:	**Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.**
P. 14:	after last paragraph:	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 15:	Section 6.5:	Change Heading:	~~_____~~ Medical Advisory Committee.
		Change Body:	~~_____~~ Medical Advisory Committee

P. 16: Section 6.7: first paragraph	Add:	**A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**
P. 16: Section 6.7: Second paragraph	Change:	—— to 60 hours
P. 18: Section A:	Change:	study drug to study drugs.
P. 20: Section D:	Add:	**Except as otherwise explicitly set forth herein,**
P. 21: Seventh paragraph:	Change:	submitted for histological examination to submitted for pathological examination
P. 27:	Add:	**Hemoglobin or Hematocrit Determination, Quant. Serum βhCG**
	Change:	Administration of —— to Administration of anti-D globulin

Informed Consent:

Section 1	Change:	———— to over 150,000
Section 2 Clinic Visits: Second paragraph last sentence:	Change:	or third visit to, visit 3,
Section 2 Clinic Visits:	Add:	paragraph 4

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.

Section 8: After last paragraph

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

AMENDMENT #2

The protocol is being amended in order to determine if any changes occur in the blood chemistry or hematology parameters of subjects following the administration of mifepristone and/or misoprostol. Blood samples will be collected as outlined below.

The following additions to the protocol are indicated.

Blood samples will be collected prior to the administration of mifepristone at Visit 1 for the following: ***(page 10 of protocol)***

Chemistry Panel (4m*L*)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3m*L*)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count

Blood samples will again be collected at Visit 3 (Day 15) for the ***same measurements listed (page 13 of protocol)*** above.

A total of twelve (12) subjects per ***each*** group ***of amenorrhea duration,*** for a total of thirty-six (36) per center will be involved in these assessments at six (6) selected centers. ***Thus,*** a total of 216 subjects from the entire study population will participate.

The notification process (contact and telephone number) Section 7.1 is modified to remove ———————— telephone number and

insert: **Dr. Irving Spitz or Dr. C. Wayne Bardin**
The Population Council, Inc.
(800) 327-8730

AMENDMENT #2 (INFORMED CONSENT)

The informed consent text was modified to reflect the additional blood collections for chemistry and hematology. ***(on pages 30, 31, 32)***.

Section 2 Clinic Visits

1st paragraph

..... 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.* In order to.....

3rd paragraph

..... 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.* If the treatment.....

Section 4 Risks and Discomforts

1st paragraph, 1st sentence

..... for the tests at the first ***and third visits*** may be.....

APPEARS THIS WAY
ON ORIGINAL

AMENDMENT #3

The protocol is being amended in order to reflect the recent data indicating an increased need for surgical procedures in Groups 2 and 3.

The additions to the protocol and informed consent are indicated.

Informed Consent

Page 25 **add:**

Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women with amenorrhea of no more than 49 days before administration of mifepristone.

There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. This excess bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.

Page 29 **delete:**

During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 percent of women.

Page 29 **add:**

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.

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.

Page 31: Section 2

Add:

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.

AMENDMENT #3 (con't)

Page 33: Section 4

Add:

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.**

last paragraph

Add:

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.

APPEARS THIS WAY
ON ORIGINAL

THE POPULATION COUNCIL

Protocol 166A/B

CENTER NUMBER ____ ____

PATIENT NUMBER ____ ____ ____

PATIENT INITIALS ____ ____ ____

APPEARS THIS WAY
ON ORIGINAL

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____ DATE ____/____/____ M D Y

STUDY ENTRY CRITERIA

INCLUSION CRITERIA:

	(check one) No	Yes
1. Is the patient in good general health?		
2. Is the patient 18 years of age or older?		
3. Did the patient request a termination of pregnancy?		
4. Does the patient agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated?		
5. Is the final estimate of duration of pregnancy based on 1) patient statement, 2) bimanual examination and 3) transvaginal ultrasound scan consistent with a time less than 64 days?		
6. Does the patient have a positive urine pregnancy test?		
7. Is the patient willing and able to participate in the study after its precise nature and duration have been explained?		
8. Is the patient a resident of the United States?		
9. Is the patient able and willing to sign an informed consent form? Date Signed: ____/____/____ M D Y		

EXCLUSION CRITERIA:

	No	Yes
1. Does the patient have evidence of the presence of any disorder which respresents a contraindication to the use of mifepristone or misoprostol?		
2. Does the patient have a history of severe liver, respiratory, or renal disease or repeated thromboembolism?		
3. Does the patient have a history of cardiovascular disease?		
4. Does the patient present with a blood pressure of >140 (systolic) or >90 (diastolic) or is the patient being treated for hypertension on a chronic basis?		
5. Does the patient have a hemoglobin level below 10g/dL or hematocrit below 30% at the day 1 visit?		
6. Does the patient use anticoagulants or have a known clotting defect?		
7. Does the patient have an IUD in place?		
8. Does the patient have insulin dependent diabetes mellitus?		
9. Is the final estimate of duration of pregnancy based on 1) patient statement, 2) bimanual examination and 3) transvaginal ultrasound scan consistent with a time greater than 63 days?		
10. Is the patient breast feeding?		
11. Did the vaginal examination reveal adnexal masses or adnexal tenderness suggesting pelvic inflammatory disease?		
12. Is there suspicion of ectopic pregnancy or threatened abortion?		
13. Is the patient older than 35 years of age and does she smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g. diabetes mellitus, hyperlipidemia, hypertension, or family history of ischemic heart disease)?		
14. Is the patient unlikely to understand or comply with the protocol requirements?		
15. Will it take the patient more than one (1) hour to reach the source of emergency medical care that serves the abortion center from her home or place of work?		
16. Will it take the patient more than one (1) hour to reach the source of emergency medical care from the abortion center?		
Does the patient qualify for enrollment in the study?		

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
1	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

DEMOGRAPHIC DATA

DATE OF BIRTH

___/___/___
M D Y

RACE/ETHNICITY (check one)

☐ 1. African American ☐ 2. Caucasian ☐ 3: East Asian
☐ 4. Hispanic ☐ 5. Other: _____

MEDICAL HISTORY

Please indicate whether the patient has any history of medical problems/surgeries in the following areas. If YES, comment in the space provided. If additional space is required, please use the comments section below.

	(check one) No	Yes	
1. Eyes, Ears, Nose, Throat, Mouth, Neck	☐	☐	_____
2. Respiratory	☐	☐	_____
3. Gastrointestinal	☐	☐	_____
4. Hepatic	☐	☐	_____
5. Renal-Genitourinary	☐	☐	_____
6. Gynecological	☐	☐	_____
7. Hematopoietic-Lymphatic	☐	☐	_____
8. Musculoskeletal	☐	☐	_____
9. Neurological	☐	☐	_____
10. Dermatologic	☐	☐	_____
11. Cardiovascular	☐	☐	_____
12. Allergies (list causative agent)	☐	☐	_____
13. Other (specify)	☐	☐	_____

APPEARS THIS WAY ON ORIGINAL

Comments (refer by item number): _____

_____

_____

PATIENT QUESTIONNAIRE

Please describe your marital status:

☐ Married Living With Partner ☐ Unmarried Living with Partner ☐ Living Without Partner

Number of years of schooling completed: ___ ___

What made you believe that you were pregnant?

_____ _____ _____

How long before you came to the clinic did you first suspect that you were pregnant?

☐ Within 1 Week ☐ 3-4 Weeks ☐ Over 8 Weeks

☐ 1-2 Weeks ☐ 5-8 Weeks

(circle one)

When you became pregnant, were you using anything to avoid pregnancy? No Yes

If yes, what were you using? _____

Other than the staff at the clinic, does anyone know about your pregnancy? No Yes

Other than the staff at the clinic, does anyone know about your decision to terminate your pregnancy? No Yes

Other than the staff at the clinic, is there a person supportive of your decision to terminate your pregnancy? No Yes

If you had elected to have a surgical abortion, what form of payment would have been used? (check all that apply)

☐ self pay ☐ medical insurance/HMO ☐ medicaid ☐ Other financial assistance

Why have you chosen to use the 'drug' method of abortion offered in this study?

_____

_____

2.1

VISIT 1 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M D Y)

OBSTETRICAL HISTORY

Is this the patient's first pregnancy? (circle) Yes No (complete below)

How many children has the patient delivered? ☐☐

How many elective abortions has the patient had? ☐☐

How many miscarriages or spontaneous abortions has the patient had? ☐☐

What was the outcome of the patient's last pregnancy? (circle one)

1) live birth
2) still birth
3) spontaneous abortion
4) elective abortion
5) extrauterine pregnancy
6) molar pregnancy

When did the patient's last pregnancy terminate? ___/___/___ (M D Y)

APPEARS THIS WAY ON ORIGINAL

DURATION OF PRESENT AMENORRHEA

Amenorrhea and gestational age are defined as the number of days beginning with the 1st day of the last menstrual period.

Date of Onset of Last Menses: ___/___/___ (M D Y) Number of days of amenorrhea: ☐☐

Transvaginal Ultrasound scan: Estimated gestational age ☐☐ days

sac size: ☐☐☐ mm

crown rump length: ☐☐☐ mm

Pelvic Examination: Estimated gestational age ☐☐ - ☐☐ weeks

Final assessment of duration of amenorrhea: ☐☐ days

Please check the appropriate group: (based on final assessment)

☐ Group 1=Amenorrhea of ≤ 49 days
☐ Group 2=Amenorrhea of 50 through 56 days
☐ Group 3=Amenorrhea of 57 through 63 days

LABORATORY STUDIES

Hemoglobin ___ ___.___ g/dL Hematocrit ___ ___ % Serum HCG ___ ___ ___ ___ ___ ___ IU/L

Blood typing (Rh status) ☐ Positive ☐ Negative Urine Pregnancy Test ☐ Positive ☐ Negative

VISIT 1 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M D Y)

PHYSICAL EXAMINATION

HEIGHT	WEIGHT	BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___ cm	___ ___ ___ kg	___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___ °C

	(check one) Normal	Abnormal	If Abnormal, briefly comment:
HEENT	☐	☐	
Chest/Lungs	☐	☐	
Cardiovascular	☐	☐	
Abdomen	☐	☐	
Skin	☐	☐	
Extremities	☐	☐	
Lymphatic	☐	☐	
Musculoskeletal	☐	☐	
Other _____	☐	☐	

PELVIC EXAMINATION

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

Comments: _____

APPEARS THIS WAY ON ORIGINAL

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
1	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

MIFEPRISTONE ADMINISTRATION

Date and time of last intake of solid food: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

Date and time of mifepristone administration: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

Lot number: JMP25524-109 Expiration date: July 1997

Clinic personnel supervising drug administration: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Clinic personnel administering mifepristone: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Patient diary should be dispensed and return visit scheduled for Study Day 3.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___°C

Did the patient report any symptoms since Visit 1? (circle one)
No
Yes (record on page 12)

Did the patient use any concomitant medications since Visit 1?
No
Yes (record on page 13)

Review patient diary for adverse events and medication use.

APPEARS THIS WAY ON ORIGINAL

ABORTION STATUS

Does the patient believe that expulsion occurred since the last visit? (circle one)
No (go to page 7)
Unsure (complete below)
Yes (complete below)

Date of expulsion: ___/___/___ (M D Y) Time of expulsion: ___:___ (24 hour clock)

Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

Abortion status was confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

*If abortion was **complete**, no misoprostol will be administered. Check appropriate box on page 7 (misoprostol not administered) and schedule return visit for Day 15.*

*If abortion was **incomplete or uncertain**, administer misoprostol and begin 4 hour monitoring.*

VISIT 2 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M D Y)

MISOPROSTOL ADMINISTRATION

Date and time of last intake of solid food: ___/___/___ (M D Y) ___ ___:___ ___ (24 hour clock)

If indicated, administer anti-RhD.

Date and time of anti-RhD administration: ___/___/___ (M D Y) ___ ___:___ ___ (24 hour clock)

☐ Not Administered

Date and time of misoprostol administration: ___/___/___ (M D Y) ___ ___:___ ___ (24 hour clock)

☐ Not Administered (specify reason)

_____

_____

Lot number: ☐☐☐☐☐☐ Expiration date: ___/___ (M Y)

Clinic personnel supervising drug administration: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Clinic personnel administering misoprostol: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

POST-MISOPROSTOL OBSERVATION PERIOD

1. Record blood pressure, heart rate, nausea, vomiting, diarrhea and abdominal pain observed during the observation period below:

Time	Clock Time	Blood Pressure	Heart Rate
0	:	/	
1 hr	:	/	

Time	Clock Time	Blood Pressure	Heart Rate
2 hr	:	/	
3 hr	:	/	
4 hr	:	/	

Symptom	Start Time	Stop Time	Severity (Circle one item each line)
Nausea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Vomiting	:	:	0=None 1=Mild 2=Moderate 3=Severe
Diarrhea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Abdominal Pain	:	:	0=None 1=Mild 2=Moderate 3=Severe

Record any medications given during the monitoring period on page 13.

Record adverse events other than nausea, vomiting, diarrhea and abdominal pain on page 12.

2. Time of expulsion ___:___ (24 hour clock) ☐ no expulsion observed

3. Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

   Abortion status was confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

4. Did the patient require additional monitoring beyond the 4 hour observation period? (circle one) No / Yes (complete page 8.1)

5. Time patient discharged from clinic ___:___ (24 hour clock)

Schedule return visit for study day 15.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	____ ____	____ ____ ____	____ ____ ____	____/____/____ M D Y

POST-MISOPROSTOL OBSERVATION PERIOD EXTENDED MONITORING

1. Why was extended monitoring indicated for this patient?

☐ Cardiovascular events (specify): _____

Was an ECG conducted? ☐ No
☐ Yes (note results/diagnosis and attach a copy of tracing)
_____

☐ Heavy bleeding
☐ Abdominal pain
☐ Other (specify): _____

APPEARS THIS WAY ON ORIGINAL

2. Record blood pressure, heart rate, nausea, vomiting, diarrhea and abdominal pain observed during the observation period below:

Clock Time	Blood Pressure	Heart Rate
:	/	
:	/	
:	/	
:	/	

Clock Time	Blood Pressure	Heart Rate
:	/	
:	/	
:	/	
:	/	

Symptom	Start Time	Stop Time	Severity
Nausea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Vomiting	:	:	0=None 1=Mild 2=Moderate 3=Severe
Diarrhea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Abdominal Pain	:	:	0=None 1=Mild 2=Moderate 3=Severe

Record any medications given during the monitoring period on page 13.

Record adverse events other than nausea, vomiting, diarrhea and abdominal pain on page 12.

VISIT 3 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE	SERUM HCG
___ ___ ___ / ___ ___ ___ mmHg	___ ___ ___ BPM	___ ___ . ___ °C	___ ___ ___ ___ ___ ___ IU/L

HCT	HgB
___ ___ %	___ ___ g/dL

(circle one)

Did the patient report any symptoms since Visit 2? No / Yes (record on page 12)

Did the patient use any concomitant medications since Visit 2? No / Yes (record on page 13)

Review patient diary for adverse events and medication use.

ABORTION STATUS

(circle one)

Does the patient believe that expulsion occurred after Visit 2 and prior to Visit 3? No (go to page 10) / Unsure (complete below) / Yes (complete below)

Date of expulsion: ___/___/___ M D Y Time of expulsion: ___ ___ : ___ ___ (24 hour clock)

VISIT 3 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M/D/Y)

PELVIC EXAMINATION

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

Status of Cervix: ☐ open ☐ closed

Comments: _____

_____

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

Confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

☐ products of conception removed from vagina/cervix

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

BLEEDING STATUS

Was medical intervention required to stop uterine bleeding? (circle one) No Yes

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

Date of cessation of uterine bleeding: ___/___/___ (M D Y)
(check against patient diary)

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

SURGICAL ABORTION

☐ Not conducted.

Date of surgical abortion: ____/____/____ (M D Y)

Abortion method: ☐electric vacuum aspiration ☐sharp curettage ☐manual vacuum aspiration

Anesthesia method: ☐local ☐general ☐conscious sedation ☐none

Pathological description of aborted tissue (attach report): _____

_____

Schedule patient post-surgical follow-up visit.

POST SURGICAL ABORTION: PATIENT STATUS

☐ Clinic visit: ____/____/____ (M D Y)

☐ Telephone interview: ____/____/____ (M D Y)

Complete vital signs below.

BLOOD PRESSURE	HEART RATE	TEMPERATURE
____/____ mmHg	____ BPM	____.__°C

Did the patient report any adverse events since surgical abortion? (circle one) No / Yes (record on page 13)

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

PATIENT QUESTIONNAIRE

Do you feel that the 'drug' abortion and side effects were adequately explained to you at the beginning of the study? (circle one) No Yes

If no, what could have been better explained? _____

_____

_____

When you were told that the 'drug' method of abortion required three visits to the clinic, was this difficult to schedule? No Yes

If yes, why? _____

_____

_____

Was your abortion experience similar to what you thought would happen? No Yes

If no, was the experience ☐ better or ☐ worse than expected?

Where were you when you had the abortion?

☐ at the clinic ☐ going to/coming from the clinic ☐ not sure/do not know
☐ at home ☐ elsewhere

Was there any problem with the timing or place of the abortion? No Yes

Was the duration of bleeding longer, shorter or about what you expected?

☐ longer ☐ shorter ☐ as expected ☐ not sure/do not know

Was the amount of blood flow more, less or about what you expected?

☐ more ☐ less ☐ as expected ☐ not sure/do not know

Was the abortion more painful, less painful or about as painful as you expected?

☐ more painful ☐ less painful ☐ as expected ☐ not sure/do not know

11.1

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MIF 006681

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

PATIENT QUESTIONNAIRE

How satisfactory was this abortion procedure?

☐ very satisfactory ☐ moderately satisfactory ☐ fair ☐ moderately unsatisfactory ☐ very unsatisfactory

Was your experience more satisfactory, less satisfactory or just as satisfactory as previous abortion experiences?

☐ more satisfactory ☐ less satisfactory ☐ just as satisfactory ☐ no previous abortion

What method was used to perform your last abortion?

☐ suction ☐ D & C ☐ other ☐ no previous abortion

What are the best features of this 'drug' method of abortion? _____

_____

_____

What are the worst features of this 'drug' method of abortion? _____

_____

_____

	(circle one)	
Would you feel comfortable taking the first medication at home?	No	Yes
Would you feel comfortable taking the second medication at home?	No	Yes
Based on your experience with the abortion procedure that you just used, would you choose the same procedure if you were considering abortion again?	No	Yes
Would you recommend this method of abortion to a friend or relative?	No	Yes

11.2

430

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CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

ADVERSE EVENTS

(check one) No ☐ Yes ☐

Were any adverse events reported by the patient during the study?

Include any changes in symptoms, signs, or laboratory values including intercurrent illnesses and exacerbations of pre-existing conditions.

Severity:
1 = Mild
2 = Moderate
3 = Severe

Action Taken:
1 = None
2 = Drug Therapy*
3 = Hospitalization

Study Drug Related:
1 = Not related
Mifepristone: 2 = Possible, 3 = Probable
Misoprostol: 4 = Possible, 5 = Probable
Combination: 6 = Possible, 7 = Probable

Outcome:
1 = Recovered
2 = Improved
3 = Unchanged
4 = Worse
5 = Death

Description	Start Date	Stop Date (Circle "C" if continuing)	Severity	Action Taken	Study Drug Related	Outcome
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				

*If treated with a concomitant drug, complete concomitant medications page.

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CONCOMITANT MEDICATIONS

(check one) No ☐ Yes ☐

Were any concomitant medications taken by the patient during the study?
If **YES,** specify below:

Medication	Dosage	*Frequency	**Route	Date Started (M/D/Y)	Date Stopped (M/D/Y) (Circle "C" if continuing)	Indication
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	

*Frequency: QD, BID, TID, QID, QOD, PRN
**Route: 1 = p.o.; 2 = s.c.; 3 = i.m.; 4 = i.v.; 5 = rectal; 6 = topical; 7 = nasal; 8 = inhaled; 9 = s.l.; 0 = other

APPEARS THIS WAY ON ORIGINAL

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

INVESTIGATOR'S QUESTIONNAIRE

PATIENT STATUS

1. Did the patient... (circle one)

   1. Complete the study?

   2. Withdraw before misoprostol? Date withdrawn: ____/____/____ (M D Y)

   3. Withdraw after misoprostol? Date withdrawn: ____/____/____ (M D Y)

   4. Become lost to follow-up before misoprostol? Date of last contact: ____/____/____ (M D Y)

   5. Become lost to follow-up after misoprostol? Date of last contact: ____/____/____ (M D Y)

Comments: _____

_____

APPEARS THIS WAY ON ORIGINAL

(circle one)

2. Given the clinical course of this patient, in the judgment of the investigator would No Yes

Comments: _____

_____

3. Given the clinical course of this patient, in the judgment of the investigator would No Yes

Comments: _____

_____

I have reviewed the complete case report form for this patient and find the data reported to be complete and accurate.

_____ ____/____/____

Principal Investigator Signature M D Y

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	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
UNSCHEDULED VISIT	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___ °C

(circle one)

Did the patient report any symptoms since the last visit? No / Yes (record on page 12)

Did the patient use any concomitant medications since the last visit? No / Yes (record on page 13)

Review patient diary for adverse events and medication use.

APPEARS THIS WAY ON ORIGINAL

Reason for clinic/office visit:

- ☐ Pain
- ☐ Bleeding
- ☐ Nausea
- ☐ Other medical problem
- ☐ Dissatisfaction with duration of abortion process
- ☐ Uncertainty about abortion
- ☐ Other

Result of visit:

- ☐ Patient requests surgical abortion (complete pages 11-14).
- ☐ Elective surgical abortion suggested by physician (complete pages 11-14).
- ☐ Surgical abortion indicated by patient's condition (complete pages 11-14).
- ☐ Ongoing medical abortion, no intervention.

ABORTION STATUS

(circle one)

Does the patient believe that expulsion occurred since the last visit? No / Uncertain (complete below) / Yes (complete below)

Date of expulsion: ___/___/___ (M D Y) Time of expulsion ___:___ (24 hour clock)

Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

Abortion status was confirmed by: ☐ vaginal examination ☐ transvaginal ultrasound

___.1

CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
UNSCHEDULED VISIT	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

EXAMINATIONS/PROCEDURES CONDUCTED
(check all that apply)

- ☐ Physical Examination
  - ☐ Normal
  - ☐ Abnormal Findings: _____
- ☐ Pelvic Examination
  - ☐ Ongoing Pregnancy
  - ☐ Incomplete Abortion
  - ☐ No Pregnancy
  - ☐ Other: _____
- ☐ Ultrasound Examination
  - ☐ Ongoing Pregnancy
  - ☐ Incomplete Abortion
  - ☐ No Pregnancy
  - ☐ Not Done
  - ☐ Other: _____
- ☐ Laboratory Tests
  - ☐ Hemoglobin ___ ___ g/dL
  - ☐ Hematocrit ___ ___ %
  - ☐ Other blood/serum analysis (attach reports)
  - ☐ Other (attach reports): _____
- ☐ Please attach pathology report for any surgical abortion procedures.
- ☐ Other (describe/attach pertinent reports on any procedures conducted)

_____

_____

___.2

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ON ORIGINAL

ILLNESSES/SYMPTOMS

Date	Illness/Symptom	Time Started	Time Stopped	Severity
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe

APPEARS THIS WAY ON ORIGINAL

PROTOCOL 166A/B

CENTER NUMBER ☐☐ PATIENT NUMBER ☐☐☐ PATIENT INITIALS ☐☐☐__

Thank you for participating in this clinical trial. Inside you will find a chart to register your menstrual symptoms and space to record medications used during the study. On the back, please list any illnesses/adverse events which occur during the course of the study.

CLINIC VISIT SCHEDULE

Visit 2 ____/____/____ (M D Y) Visit 3 ____/____/____ (M D Y) Additional Visits ____/____/____ (M D Y) ____/____/____ (M D Y)

IF YOU NEED EMERGENCY CARE DURING THE STUDY, CALL *(days)* _____

(evenings, weekends) _____

Call one of these numbers if you have heavy menstrual bleeding, fever, severe abdominal pain or other medical problems.

SUBJECT'S DIARY

MENSTRUAL SYMPTOMS

Mark an 'X' in the appropriate box for each symptom which occurs during the study.

STUDY DAY	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Date															
Heavy Bleeding															
Normal Bleeding															
Spotting															
Pain/Cramps															
Abortion/Expulsion															

*Day 1 is the day of taking mifepristone.

APPEARS THIS WAY ON ORIGINAL

MEDICATION USE

Medication	Total Daily Dose	Date Started	Date Stopped (circle C if continuing)	Reason for Use
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	

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

NON-PARTICIPANT PATIENT QUESTIONNAIRE

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

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

Age: _____

Ethnicity/Race:

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

Social Circumstances:

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

Have you had an induced abortion before today?

☐ Yes ☐ No

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

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

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Continuation of Protocol 166A

Appendix C

Part E. Publications Based on the Study