abortion providers and to share with you our experiences with mifepristone.

The National Abortion Federation was established in 1977 as a professional association of abortion providers committed to ensuring that abortion services remain safe, legal, and accessible to all women. NAF's members provide about half of all abortions in the United States each year.

Several NAF members, including myself, participated in the Population Council's clinical trial of mifepristone. Our experience matched that reported in other countries. Mifepristone is a safe and effective forum of early abortion which should be an option for women wishing to terminate a pregnancy.

As you are aware from this morning's presentations, mifepristone blocks the action of progesterone, a hormone needed to sustain a pregnancy, and in trials to date has been proven safe and effective in terminating early pregnancy.

Our experience during the clinical trials was consistent with the experience in Europe. The drug was quite safe and effective and women who participated were generally very positive about this method.

I believe one of the reasons medical abortion with mifepristone has been and can be successful relates to the thorough counseling that both providers and women

receive. As a provider I knew what to expect and how to care for women who were going through this process. There were no unexpected side effects and at no time did I feel that my patients were in danger. Equally as importantly, my patients knew what to anticipate and as a result felt confident using the drugs.

Many of the women in the clinical trial at my site expressed their strong support for the drug because it allowed them to participate in and have a sense of control over this experience. It is worthy to note that, in my opinion, my patients did not feel themselves to be pioneers or advocates, rather, they were women who had requested a pregnancy termination and who, after thorough counseling, simply felt that this method best met their needs.

As a doctor I believe that not only is mifepristone safe and effective but for some women it may be the most appropriate means of terminating a pregnancy. In some settings, especially in resource poor settings such as the developing world, legal access to mifepristone may result in improved health care for women who are exposed to and some times die from unsafe and ineffective abortions. Approval by the FDA of mifepristone would undoubtedly improve access to safe and effective abortion worldwide.

As you know, mifepristone is the culmination of many years of research. It has been tested in both

developing and industrial countries by the Population Council and the World Health Organization. The governments of France, England and Sweden have all approved the use of mifepristone after their own rigorous clinical trials and worldwide over 200,000 women have used this non-surgical method.

Mifepristone could also be used in treating several other conditions related to pregnancy and other medical problems such as breast cancer. With so many potential uses and impressive and efficacious record we hope that mifepristone will be favorably reviewed by the Food and Drug Administration. Thank you.

DR. CORFMAN: The next speaker is Susan Wysocki, speaking for the National Association of Nurse Practitioners in Reproductive Health.

National Association of Nurse Practitioners in Reproductive Health, Susan Wysocki, R.N.C., N.P.

MS. WYSOCKI: Members of the Advisory Committee on Reproductive Health Drugs, good afternoon. I am Susan Wysocki, President of the National Association of Nurse Practitioners in Reproductive Health and I am a certified women's health nurse practitioner.

NANPRH is a national organization representing nurse practitioners in obstetrics, gynecology, and women's health. We have no conflict or financial interest in this

product.

You have heard testimony about the medical safety of mifepristone. I would like to talk to you today about the use of mifepristone from a nurse's perspective.

Nursing's tradition is to care for patients from a holistic perspective, taking in consideration a patient's physical, emotional, and spiritual needs. Mifepristone, while not an ideal method of abortion for every woman, does have some distinct advantages and go beyond its medical safety.

In contrast to some who argue that medical abortion is too easy in most respects medical abortion is much less easy. There are three or more visits to a physician and two or three days during which a woman experiences the termination of her pregnancy versus one visit for a surgical abortion which lasts a matter of minutes and one visit for the follow-up exam.

One might ask why a woman would choose a medical abortion over surgical abortion. The difference is who is in control. With medical abortion the woman swallows the pills from her own hand, it is her body that is doing the work of aborting a pregnancy, she is a more active participant of the process, she experiences the abortion, she feels her body respond.

My colleagues who have provided nursing care to

these women report that even when women experience side effects the control they gain from being part of the process greatly outweighs other considerations. My colleagues report that these women seem to integrate the emotional and spiritual aspects of abortion during the few days after they have taken mifepristone. The patient's reactions seem to be evidence of a greater ownership of the process.

Medical abortion is not for every woman seeking abortion. Regardless of the method of abortion chosen, surgical or medical, the vast majority of women process the emotional and spiritual aspects in a very short period of time, there are exceptions of course. Abortion does not solve the grief of a failed or abusive relationship, it won't make the time a woman had intercourse in a forced or compromised situation away, it does not solve a dysfunctional family environment or a partner's drinking problem.

As nurse practitioners in the field of reproductive health we help to prevent unintended pregnancy, whether it is helping an individual to practice abstinence or providing effective contraception. We provide women centered care in order to help promote self-esteem, to say "no" when she wants to, insist on the use of condoms, and let her make her own choice if she becomes

pregnant unexpectedly.

There is no perfect method of contraception for the over 30 years that a woman can conceive, not one. Over 50 percent of women who become pregnant unintentionally are using contraception. Women's motivation, together with the care provided by health care providers across this country contributes to the miracle that there are not millions more of abortions. The odds are overwhelming.

Based on mifepristone's effectiveness and safety NANPRH requests that this committee approve its use. American women should have this option for terminating their own pregnancies. Thank you.

DR. CORFMAN: The next speaker is Donna Gary for the National Council of Jewish Women.

National Council of Jewish Women - Donna Gary

MS. GARY: Good afternoon. My name is Donna Gary. I am a National Vice President of the National Council of Jewish Women. There is no financial connection and no one has paid my expenses. I am a volunteer.

The National Council of Jewish Women is a non-profit volunteer organization with 90,000 members in over 500 communities nationwide. I have come before you today to urge swift approval of the New Drug Application to the FDA for mifepristone to be used for medical abortion.

The National Council of Jewish Women strongly

supports the enhancement of reproductive health options for all women. Mifepristone has been proven worldwide to be aa safe, early and effective non-surgical method of abortion. Clinical trials conducted over the last decade in France, Sweden, and the United Kingdom, along with additional clinical trials in the United States, have consistently shown that mifepristone is a viable non-surgical early abortion method.

As evidenced by the nearly 200,000 women in Europe who have chosen to use mifepristone, women trust this procedure, and many want to use this method as an alternative to surgical abortion when terminating a pregnancy. Don't women in the United States deserve the same reproductive health options as women in these countries?

We believe that FDA licensing of mifepristone will result in a significant step towards improving reproductive health options for women in this country. The introduction of mifepristone would have a profound effect on women's health in the United States. Not only would it provide women with a safe, non-surgical method to terminate pregnancies early on, but mifepristone could also be used in treating a wide range of medical conditions affecting women including breast cancer, endometriosis, and uterine fibroids.

The availability of mifepristone in the United States would likely improve access for women seeking abortions. Often women must travel long distances to obtain an abortion and often endure harassment and violence when seeking clinic services. Making mifepristone available in this country would give women the option of locating practitioners closer to their homes who are wiling to provide medical abortions.

The National Council of Jewish Women strongly supports "every female's right to reproductive choice, to safe and legal abortion, and to the elimination of obstacles that limit reproductive freedom." On behalf of the National Council of Jewish Women, I strongly recommend approval of mifepristone for licensing in the United States. Thank you for this opportunity to testify today.

DR. CORFMAN: The next speaker is Janice Erickson for the National Organization for Women.

National Organization for Women, Inc. - Janice E. Erickson

MS. ERICKSON: Thank you very much. I am Director of Government Relations and Public Policy for the National Organization for Women. I am speaking here today for the NOW Foundation. We have no financial interest in this drug.

NOW is the largest feminist organization in the

country, with over 275,000 members in 700 chapters throughout all states. We have a long history of advocacy for keeping abortion safe and legal and accessible.

NOW believes that mifepristone should be found safe and effective by this advisory committee and should ultimately be approved by the Food and Drug Administration for general use in the United States. Sixteen years of testing and clinical experience with mifepristone in Europe and America have provided abundant evidence that the drug is effective in terminating in early pregnancy with very few side effects.

Mifepristone has been safely and successfully used by nearly 200,000 European women, approved by the governments of France, Sweden and the United Kingdom, the RU 486 story is one of sound medical technology responding effectively to meet vital patient needs.

We are fortunate in the United States to be able to benefit from the European experience. It is our understanding that the U.S. clinical trial findings are very comparable to those from France as regards safety and efficacy.

We expect that this advisory committee's conclusions will be based on a rigorous examination of the available French and U.S. data and the final decision by the Food and Drug Administration will be based exclusively

on strong scientific evidence in favor of approval for mifepristone for general use.

Advances in the medical research of reproductive health have been tragically slowed and even stopped in this country. Women and the general public have suffered immeasurably as a result. We must move forward. A majority of the American public does not want to see safe and effective improvements denied to anyone, as private surveys show.

Even a substance proportion of the abortion rights opponents surveyed are supportive of early medical abortions. A safe, effective, early abortion drug may begin to heal the wounding divide that has been created in the public over this procedure.

The problem of accessibility to abortion services has been a vexing one for reproductive rights advocates. Mifepristone offers the best solution yet to expanding the pool of providers and ultimately to bringing the cost of the treatment well within the means of most women.

Successful trials on mifepristone as a method for early abortion in Vietnam, Cuba, China, and India by the Population Council as well as trials by the World Health Organization in Chile, Germany, Hungary, and other parts of the world show that there are no differences in the rates of safety, efficacy, and acceptability when comparing

racial or ethnic groups. This would indicate that there would be wide acceptance in use of this important drug worldwide.

As an organization concerned about the health of all women we are eager to see this country move forward. Such critical health problems as endometriosis, breast cancer, uterine fibroid condition, which effect millions of women could potentially benefit from further research on mifepristone. An aging U.S. population could also benefit from the other research and applications that could be found on this drug.

Finally, it should not be overlooked that mifepristone, through expanded research and development in the United States could make a tremendous contribution to international contraception and fertility treatments, especially in the developing world.

America's incomparable medical research infrastructure and financial resources, coupled with FDA's rigorous and independent regulatory function can help ensure for the world a safe and effective drug through mifepristone. Thank you.

DR. CORFMAN: The next speaker is Cynthia Pearson, speaking for the National Women's Health Network.

National Women's Health Network - Cynthia A. Pearson

MS. PEARSON: Good afternoon. My name is Cindy Pearson, Executive Director of the National Women's Health Network.

The Network is a nonprofit women's health advocacy group, supported by over 14,000 and 400 organizational members. The network does not accept financial support from pharmaceutical companies or manufacturers of medical devices and has no financial interest in this.

Ellie Smeal aptly described the feminist community's some times critical view of the medical profession and commonly used drugs, devices, and procedures. As many of you know all too well, if there is any one organization that exemplifies that attitude it is the National Women's Health Network.

[Laughter.]

I am here to tell you today that we believe it has been well demonstrated that mifepristone used with misoprostol for early abortion is effective and its short term safety in the women's study is well documented.

We also believe that abortion is a woman's right and the medical profession has a duty to provide abortion in a safe and acceptable manner. We would like to focus our remarks in this short time today on the safety allegations made by groups which, unlike the Network,

oppose abortion.

The Network is a diverse organization. More than half of the members of our board of directors are women of color. The FDA in the past has heard from anti-abortion groups asking that the FDA not approve mifepristone and misoprostol because it is unsafe for women of color.

It is true that women of color were not represented in the pivotal French trials and the Network previously raised questions about the unknown effect of these medications in women of color but we were happy to hear, presented today, data which demonstrated that women of color, who made up approximately one-third of the women in U.S. trials, describe their experience in exactly the same way as did white women.

While we understand that these are not medical reports we are willing to trust women's own description of their experience and are reassured by these data. We believe that there is no reason at this time to oppose approval because of concerns about women of color's safety.

Anti-abortion groups have also asked that the FDA not approve mifepristone plus misoprostol because it will increase the likelihood of developing breast cancer. Breast cancer is an issue on which the Network is expert. In January of 1994 we were the first women's group to release a physician paper on the possible link between

abortion and breast cancer.

We reviewed the evidence and found that the link between abortion and breast cancer had not been established. In contrast to Dr. Brind's description earlier this afternoon that the preponderance of the evidence demonstrates an increased risk of breast cancer our review found that there are over 70 studies which have data on abortion and breast cancer. Fewer than 30 of these studies have been published to date and of those published about half found an increased risk while half found no increase at all.

Also in contrast to Dr. Brind's claim it is our understanding that another meta-analysis, one which will include all data, both published and unpublished, is being conducted and that it appears to be finding no increased risk.

To claim that abortion increases the risk of breast cancer is to misrepresent data in an effort to frighten women and we believe that the FDA need not even consider this issue when deciding whether or not to approve mifepristone.

Finally, anti-abortion groups have also claimed that mifepristone plus misoprostol should not be approved because there are or maybe long term risks associated with its use. The Network has consistently raised questions

about the long term safety of drugs given to women. Our typical concerns are much diminished in this situation.

Mifepristone is intended to be used once, or at most a few times, and has a short half life. Long term effects are most often caused by drugs which are used long term, for example, Cytotec which we have just heard so much about typically is used on a long term basis.

Misoprostol has -- given this reassuring information we believe that approval should not be delayed while we search for the final answers about long term safety. The Network believes that it would be prudent for the FDA to require post-approval studies with long term follow-up but we want to emphasize thought that our recommendation is made on general principles, not because of specific concerns based on any biologically plausible mechanisms.

We also want to re-emphasize that we believe there are adequate safety data to approve mifepristone and misoprostol now. Mifepristone is an effective method of abortion which expands the options of women desiring pregnancy termination. We applaud its consideration by this committee and recommend its approval.

DR. CORFMAN: Next speaker is Susan Hill for the National Women's Health Organization.

National Women's Health Organization - Susan Hill

MS. HILL: Good afternoon. I come to you today as an abortion provider from the trenches. I am the President of National Women's Health Organization, a private company that manages eight abortion clinics in eight states. The mission of our company since 1976 has been to provide abortion services in under-served areas of the United States.

We were the first abortion provider in rural Indiana in 1978. We were the first abortion clinic in Delaware in 1978 and the only clinic in that state for 10 years. We were the first abortion clinic in North Dakota in 1981 and we are still the only clinic in the state. In 1995 we opened an abortion clinic in Jackson, Mississippi. We are one of the two remaining clinics in the state of Mississippi.

In January 1973, when I started working in the abortion service field, I believed that by 1996 American women would be able to receive abortion services in their private physician's office with all the privacy and confidentiality that that would provide. I could not have guessed or dreamt that instead of more providers there would be less and that their very lives would be threatened everyday by providing abortion services.

Today, American women obtaining the legal medical service of abortion are put through a test that no American

could believe until they, their wives, daughters, or friends are in need. Women in Mississippi and North Dakota obtain services under restrictions that no other medical service would ever be required to have.

In Mississippi, the poorest state in the country, women are required to have a state produced consent read to her face to face 24 hours before the procedure by a physician only. The state requires color pictures of fetuses along with a script, produced by politicians not physicians, to be read to the woman.

Women come from the Mississippi delta, the poorest region in the state, which is four hours away from Jackson. They sleep overnight in their cars because they have no money for a hotel. I have personally counseled a family from the delta whose 11 year old had been raped and was in the clinic for a procedure. We found that family the next morning at 5 o'clock sleeping with that daughter and 2 other daughters in their car waiting to comply with the 24 hour waiting period. Certainly no American woman should be forced to obtain legal medical services in such a punitive manner.

Women in North Dakota drive 10 and 12 hours from the most distant parts of the state to get to our clinic in Fargo. They pass many cities and towns where there are doctors but no abortion services. They face the same

restrictions and hardships that women in Mississippi face.

In the 23 years that I have provided services I have watched women between the ages of 10 years old to 50 go through hell to obtain abortion services. They have been screamed at, threatened, pushed, evacuated from clinics right after surgery because of bomb threats, followed home, harassed at work, and still they have made a choice that is given to them by the law of the land.

More importantly, I believe I am the only person testifying today that has worked personally with a physician who was killed for providing abortion services. Dr. David Gunn was a physician at our Georgia, Southwest Georgia rural clinic, for eight and a half years. He was forced to drive 1,000 miles a week to 5 clinics in the South because no other doctors would provide the service.

Our Columbus, Georgia clinic, open since 1974, has never had a local physician. Our Fargo clinic, open since 1981, has also never had a local physician. Our Indiana clinic has not had a local doctor since 1986. Our Mississippi clinic has no local physician. Surprisingly, our Orlando clinic in a large metropolitan area, has not had a local physician since last year.

Doctors are willing to provide abortions but they are not willing to become targets. May I just finish one last thing please? I believe with all my heart that

mifepristone could stop this ghettoization of abortion providers. Women would finally have the option of privacy in their choice. Staff and physicians would no longer be targets but once again medical professionals providing medical services.

When I first heard about RU 486, I went to France to observe its use. The French physicians asked our reactions after two days of observations. Our first response was, "It's so quiet and peaceful. This is the way medical services should be done."

On behalf of the 600,000 women our clinics have served from North Dakota to Mississippi to North Carolina, I beseech this committee to give to women the privacy and respect that this drug would ensure them. I have observed many times that women having illegal abortions in this country were afforded more privacy than women have had with legal abortion.

Please give women back the dignity that they so deserve in this country. Thank you.

[Applause.]

DR. CORFMAN: Next speaker is Ann Kolker for the National Women's Law Center.

National Women's Law Center - Ann Kolker

MS. KOLKER: Good afternoon. I am Ann Kolker, Public Policy Director at the National Women's Law Center,

a legal and public policy organization that for over 20 years, has been working to secure equality and equal opportunity for women in the work place, in educational and family settings, and in their access to health care, income and family support services. I appreciate the opportunity to appear before you today.

Central to women's equality is access to safe and legal abortion but as we have just heard, so eloquently, over the years a vocal minority has waged a relentless battle to make abortion illegal again, to intimidate women seeking services, and to drive providers out of practice, through harassment, violence, and threats to their families.

The submission by the Population Council of an NDA for mifepristone and the approval process now underway here at the FDA have a chance to change this landscape dramatically. The Center strongly supports FDA's efforts to review carefully and thoroughly this NDA and determine whether mifepristone, in combination with misoprostol, is safe and effective. We fully hope that the FDA will come to the same conclusion that has been reached by experts in France, Great Britain, and Sweden where the drug has been available for several years, if not more.

We cannot overstate the value to women of the availability of safe medical abortion as an alternative to

surgical abortion. Use of an abortifacient drug can take place in a physician's office rather than at a clinic. Thus, women will be spared the kinds of traumas that we have just heard so eloquently described, blockades and taunts.

The statistics are very very chilling. Indeed, in recent years nearly 40 percent of clinics experienced some form of severe violence and nearly 20 percent of clinic staff reported death threats and home picketing.

Assuming that the FDA determines that mifepristone is safe this method of non-surgical abortion has important and favorable implications for the health of women seeking early termination. Many women, as we have already heard, seeking early termination may fear the invasive nature of surgery along with the prospect of anesthesia. Taking several pills induces the abortion which then occurs in the same way as a miscarriage.

The fact that mifepristone works early in pregnancy, when abortion is safest, is also advantageous. The availability of the drug for use during the first seven weeks of pregnancy, or nine weeks at most, will act as an incentive for women seeking to end an unwanted or unsafe pregnancy to seek medical help in the early weeks.

The approval of mifepristone stands to have a beneficial effect on the number of providers willing to

perform abortions in this country, a change that has positive implications for women's health as well.

A recent survey by the Kaiser Family Foundation found that at least one-third of OB/GYNs would add abortion to their practice if involved prescribing medication such as mifepristone rather than surgery.

Ultimately, the availability of more physicians willing to provide abortions will reduce travel time and arrangements, particularly for women in rural areas, thus, enabling these women to undergo the procedure at an earlier point in the pregnancy when it is safest.

the National Women's Law Center, which has worked with FDA over the years on newly developed methods of contraception, know that product approval decisions are based on careful review of clinical trials, scientific data and research articles by physicians and other experts.

Some who have appeared before this advisory committee earlier today presented claims and charges about mifepristone that are not supported by clinic trials and the experiences of both women in this country and overseas who have successfully and safely used this non-surgical abortion method for many years.

Thus, we urge this committee to be guided in its decision making about mifepristone by the scientific evidence presented by the Population Council's NDA and

related materials and not on ideologically motivated claims that are without scientific merit.

American women eagerly await your recommendation and hope that before the year is over the FDA will render a favorable decision on this important medical breakthrough. Thank you.

DR. CORFMAN: Next speaker is Dr. Louviere from Northeast Waterloo Family Practice.

Northeast Waterloo Family Practice - Mark Louviere, M.D.

DR. LOUVIERE: Thank you. I hope God or whoever we believe in isn't telling us something with that thunder out there.

[Laughter.]

My name is Mark Louviere. I am a board-certified family practice physician who does quite a bit of OB, about 150 deliveries a year, in Waterloo, Iowa. I am on the clinical teaching staff at the University of Iowa College of Medicine.

I have been told, and I hope it is true, that my expenses will be paid for by the Life Issues Institute, even though I am pro-choice I find it very interesting that they are willing to do that. I am ethically and morally opposed to abortion, have not done or will ever do abortions but for reasons I do not want to go into here, I

believe that it should be safe and legal.

I am the infamous Iowa connection that has been referred to many, many times today. I will tell you that story. In November of 1994 I was called to the Alan Hospital Emergency Room in Waterloo, Iowa, for a woman who was bleeding due to a miscarriage and was in obvious shock.

A blood test showed that she had lost between one-half to two-thirds of her blood volume. For those of you who understand this, her hemoglobin was 5.8 and her hematocrit was 17.3. Her blood pressure was 90/60, her pulse was 120, she was in obvious shock.

I had thought she was having an incomplete miscarriage, but her husband took me into the hall and told me that she had taken RU 486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate D&C.

Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.

Even later that evening, 2 hours post-transfusion of those 2 units, her hemoglobin was still 6.8 and her hematocrit was 20 something. She required two more units

of blood because she was still orthostatic and symptomatic.

Because I aware of the clinic trial, the following day I called Planned Parenthood of Greater Iowa in Des Moines and notified them of what happened. I sent a complete copy of her medical chart to Des Moines. I would have thought nothing more about it and would not be here today if it wasn't until about 10 months later I read an article in the Des Moines Register that Planned Parenthood of Greater Iowa had reported, and I quote, "The clinic test of the abortion pill has ended in Iowa with no complications reported among 238 women who ended unwanted pregnancies without surgery," end of quote. They did not say anything about unsuspected complications or complications with the trial, they said there were, "no complications among 238 women." This was a lie to the people of Iowa.

I had two concerns. One was that Planned Parenthood was obviously lying to the media and, therefore, the people of Iowa. My second concern was that I had idea if Planned Parenthood was lying to the Population Council and, therefore, to the FDA.

This became a news story because I wrote an editorial, as I often do, to the Des Moines Register. Instead of printing it as a guest editorial they made it into a news story regarding my findings which was picked up

by the Associated Press and reported across the country.

The response by Planned Parenthood in this news story was rather disingenuous. They said that what they meant was that there were no unsuspected complications. I mean, I wonder if she would have died, I mean we know that that may be a complication so that would not have been unsuspected but they also said that there were no complications to the carrying out of the trial and I do not know what that means, whether people dropped their pill or they did not get hit by a car walking across the street.

I did call The Population Council and informed them of my findings and they had been told. They told me that Planned Parenthood of Greater Iowa had informed them.

Because of my concerns about Planned Parenthood of Greater Iowa lying to the media and perhaps lying to the Population Council, I have concerns about the use of RU 486 by physicians without appropriate follow-up. My concern is that when RU 486 is used some patients may experience the same untoward complications because it is used in an outpatient setting. There is no guarantee that once patients receive RU 486 they will follow-up appropriately if there is a complication.

In summary, I am concerned that all of the complication of RU 486 were not reported to either the media or to the FDA. I am also concerned that the non-

surgical approach to abortion, due to poor patient compliance, for a number of reasons will lead to more complications than actual surgical abortion.

I thank the committee for this opportunity to appear and report my findings. Thank you very much.

DR. CORFMAN: I have been told that if we do lose power because of the storm there will be emergency lights. It will be dim but we will be able to see what is going on.

The next speaker is Mary Jasinski Caldwell for Pharmacists for Life, International.

Pharmacists for Life, International - Mary Jasinski Caldwell

MS. CALDWELL: Good afternoon. On behalf of the officers, board of directors and thousands of supporters for the Pharmacists for Life, International, I wish to thank the advisory panel for consideration of our oral testimony.

PFLI is a professional pharmacy association whose unique scope and mission is exclusively set out to defend and stand for the integrity, dignity, and sanctity of all human life from the moment of fertilization to natural death.

We differ from almost all other professional pharmacy associations in that we have no economic motive for existence.

The presumptive reason for today's hearing is to inquire into the petition for approval by the full Food and Drug Administration for use of mifepristone as an abortifacient in the United States. I am here to express the complete and total opposition and protestation by our members and supporters to any such approval for it is totally contrary to all pharmacy codes of ethics and standards from the time of Hippocrates to the present day.

Pharmacy is a life saving profession and nearly year after year we are rated as the most trusted profession by the public in an annual Gallop poll. It is difficult to comprehend that we would preserve that place of pride for very long should it become well known that we did little, if anything, to prevent introduction of mifepristone into the American health care system.

The literature on mifepristone, rightly called a "human pesticide," by the late world-renowned geneticist Dr. Jerome Lejeune clearly shows that it is hardly anything simple, effective, or safe, quite to the contrary. The extensive testing of mifepristone abroad, as well as the cryptic like secretive trials that were run here in the United States with most funding coming from the agenda driven Buffet Foundation, shows mifepristone is rather ineffective. The recent secretive trials in the United States yielded one subject who lost four pints of blood and

nearly bled to death.

On the question of privacy, mifepristone requires three to five office visits by the woman to a licensed abortion clinic, a number of invasive examinations and tests and the taking of up to a five drug chemical cocktail. Mifepristone has a failure rate to 20 to 40 percent alone, necessitating use of a second drug, the prostaglandin Cytotec, which still results in a 5 percent abortion failure rate requiring 1 in 20 women to undergo yet another abortion procedure.

The many short term adverse effects include bleeding of up to 42 days, cardiovascular maladies, fatigue, abdominal pain, nausea, dizziness, and syncope. There are unknown long term side effects due to these drugs and the use on the womb, ovaries, adrenal glands, central nervous system, and the developing embryo.

Dr. Renee Kline summarized her position on mifepristone this way, and I quote, "Although I support a woman's right to a safe and legal abortion with good counseling, I am emphatic that this dangerous second rate drug is not a positive decision to a woman's decision making."

It is odd that the FDA consider the application for this chemical from an organization whose own non-profit status is the current subject of scrutiny by assorted

parties and which itself is not a pharmaceutical manufacturer but rather a funded arm of the Rockefeller Foundation whose scope and vision includes negative population growth. Would mifepristone be the great wonder drug and marketing home run as its promoters say it is drug manufacturers would be fighting to introduce it.

With all of the foregoing in mind as well as the awesome grave and moral and ethical responsibility the FDA has for the approval of safe and effective drugs which are meant to heal and preserve life it would be a black letter day in the United States should this panel recommend approval of mifepristone to the full DEA.

We emphatically and categorically petition you to reject any approval of mifepristone for use in the United States of America. Thank you very much.

DR. CORFMAN: The next speaker is Gloria Feldt, speaking for the Planned Parenthood Federation of America.

Planned Parenthood Federation of America, Inc. - Gloria Feldt.

MS. FELDT: Good afternoon. Thank you for allowing me to speak. I am Gloria Feldt, President of Planned Parenthood Federation of America.

Each year our nearly 1,000 health care centers nationwide provide reproductive health care, education, and counseling services to over 5 million individuals. For 80

years family planning services to enable people to prevent unintended pregnancies and plan wanted ones has been the heart and soul of our work.

Planned Parenthood centers provide abortion services to about 130,000 women each year. Six of our centers were part of the mifepristone clinical trials.

Every time there is a news story about medical abortion women call Planned Parenthood, the name they trust. Women ask us about medical abortion and we have to tell them, "Yes, we know it's available in Europe but we can't offer it to you here." These women are understandably frustrated.

Political reasons, not medical reasons, stood in the way of introducing mifepristone in France at first until their public health service declared it to be the, "moral property of women," and went forward with it.

We are gratified that mifepristone, which has been used successfully by more than 200,000 women in Europe, has finally reached the point of FDA consideration and mifepristone should be reviewed in the same manner as any other drug.

Strident opposition from those religious/political extremists has chilled and deep frozen critical research and testing for all kinds of health services that could help protect the fertility and lives of

women and might also contribute to medical treatment for other conditions. I know you must be under tremendous pressure from the opponents of mifepristone and I hope that this hearing today will mark the beginning of a new era for women as they strive to plan and space their children responsibly.

The acceptability study presented today by the Population Council backs up what Planned Parenthood's physicians, nurses, and counselors have observed. Most women were quite satisfied with medical abortion. Because of the in depth counseling that they received women said they were prepared for the mifepristone process.

The side effects some women experienced did not surprise or scare them. For most women, in fact, the procedure was what they expected or better than they expected. I might add that the patient in Iowa whose situation was not exactly accurately described reported that she herself was satisfied with the procedure. Certainly there is no drug or medical procedure without some level of risk which is why we have the FDA to assess those things for us.

Unintended pregnancy itself is a tremendous problem in the United States and carries with it health risks far greater than mifepristone. We at Planned Parenthood do our best to serve women with contraceptive

information and services but it is imperative that America women faced with unintended pregnancy have access to the newest and safest methods of ending a pregnancy as early as possible.

Making mifepristone available will also eventually increase women's access to abortion services and make harassment and violence less effective as a weapon against women and health care professionals who serve them. That is exactly what the opponents of mifepristone are most afraid of.

In summary, our experience with mifepristone was what we at Planned Parenthood and the women we serve expected. For the overwhelming majority of women mifepristone proves safe and effective. The complications that arose were the ones that were expected and were manageable. Serious complications were rare. Most women were satisfied.

We at Planned Parenthood look forward to offering medical abortion using mifepristone. We are ready. American women are ready for this safe and effective method. Thank you.

DR. CORFMAN: Next speaker --

DR. AZZIZ: If I could have a question for a second.

MS. FELDT: Certainly.

DR. AZZIZ: Could you clarify for a second what kind of problems that you encountered in Iowa perhaps? Clearly that was a problem either in reporting or in access to the patient's follow-up so perhaps if you could give us a little more enlightenment.

MS. FELDT: Yes. The exact situation was this, the patient was unable to return for her second follow-up exam, the third visit, due to weather conditions. She experienced this problem. Had she been able to return for the appointment that she had it is probable that a surgical abortion would have been provided for her at that time and it is highly probable that that would have eliminated the problem or she would not have had the problem that she had.

The complication was in fact, immediately in fact the same day, reported to the Population Council which the next day reported it to the FDA.

DR. AZZIZ: I guess what I am unclear as is was the hemorrhage event related to RU 486 treatment 2 weeks prior or was it related to a spontaneous miscarriage that occurred after a failed termination?

MS. FELDT: No, she had taken mifepristone and she had not been able to return for the third exam in the series of three.

DR. AZZIZ: The bleeding episode occurred how soon after the RU 486 was administered? Two weeks? Three?

MS. FELDT: Let me look. I actually have a time table of events which I would be happy to leave with you which would probably be better than my trying to answer it for you.

DR. AZZIZ: My only concern and we don't have to is whether the bleeding episode, which is not uncommon, severe bleeding, with incomplete abortions that occur and this may be the case as opposed to a complication related to the medication and for the committee that is an important issue.

MS. FELDT: I understand. The bleeding --

DR. LOUVIERE: Approximately two weeks later she was not able to get to her appointment. If she had been able to get to her appointment I believe she would have been managed appropriately. I had no problem with that. My feeling was that the article in the paper said that there were no complications --

[Dr. Louviere is speaking from the audience without a microphone, unable to hear all of comment.]

MS. FELDT: And it was at that approximately two week point. I do not know if that answers it. I would be happy to provide you with the exact time line of how things occurred if you would like to have it.

DR. AZZIZ: Thank you.

DR. CORFMAN: The next speaker is Dr. Lynn

Borgatta for Planned Parenthood of Westchester and Rockland.

Planned Parenthood of Westchester and Rockland, Inc. - Lynn Borgatta, M.D., M.P.H.

DR. BORGATTA: Good afternoon, members of the committee. It has been a long afternoon, we are almost at the end.

I am a board-certified obstetrician/gynecologist and a public health physician. I am also a dues-paying member of some of the mainstream organizations that have presented earlier such as the American College of OB-GYN, American Public Health Association, and American Medical Women's Association. I am a clinical associate professor of OB-GYN at New York Medical College.

I am here today representing Planned Parenthood of Westchester, Rockland and Putnam Counties, a large Planned Parenthood affiliate in suburban New York where I am medical director. I am also representing the Association of Reproductive Health Professionals.

Our Planned Parenthood was one of the 17 sites for the mifepristone trials in this country and I would like to present some of our experience. We were honored to participate in this very important research and we support the approval of mifepristone.

Many of my feelings are very similar to those of

Dr. Newhall who presented her experience so beautifully this morning. As experienced providers of surgical abortion services, and I have 20 years of experience myself, Planned Parenthood knows the safety of their surgical procedures and the high level of satisfaction of our patients who undergo surgical abortions.

Early surgical abortion is so safe that it is really hard to improve on such a good record. Mifepristone, however, provides an important alternative. Since mifepristone has been used by so many women before we were able to draw on the experience of others in setting up our own program. Our program did not require any additional facilities other than those that we already had as provider of many women's medical services including pre-natal care and family planning.

We found that the mifepristone abortion process is, of course, very different from a surgical abortion and we found that it was effective for almost all of the women and that there were no unexpected side effects.

Our clientele was diverse in ethnic, socio-economic, and age distribution but all of the women found the side effects tolerable and most of them found them to be relatively minor and of short duration. Women said things like, "Well, yes, I have pretty strong cramps but I have had cramps before. I have bleeding but I have

experienced bleeding before." When they were all done they said, "I did it."

The events and possible complications which may occur during and after a medical abortion a similar to those that may occur during and after a miscarriage. The doctor and the medical professionals who are competent at managing the events during a miscarriage have the skills necessary to manage mifepristone abortions. Since many physicians, besides just OB/GYNs, are trained to assist women who have miscarriages the availability of medical abortion can improve access to early abortion and, as you know, early abortion is the safest.

Ectopic pregnancy has been mentioned and the most successful treatment of ectopic pregnancy occurs when early diagnosis has been made and anything that brings women in earlier will assist in the diagnosis of early ectopic pregnancy.

Mifepristone was very acceptable to our patients and our staff. Those who choose it were grateful to have this non-surgical alternative and we must continue to disappoint women who want to use the method and are unable to.

In many other areas of medicine we have situations where there are several possible treatments and in the United States women participate in decisions about

their care in consultation. They decide based on the risks, benefits and acceptability and treatments are individualized.

Mifepristone provides a safe and effective way and it increases the number of choices and the natural choice is to have a choice.

DR. CORFMAN: The next speaker is Marie Bass, speaking for the Reproductive Health Technologies Project.

Reproductive Health Technologies Project - Marie Bass

DR. BASS: Thank you very much. I am Marie Bass. I am here today on behalf of the Reproductive Health Technologies Project. This project came into being almost 10 years ago because of this very product. A group of people from a very, very diverse set of backgrounds and affiliations including leaders from international population groups, family planning organizations in this country, women's health groups, feminist groups, women of color groups, there was almost nothing that everybody could agree on except that this product and the whole class of drugs to which it belongs were not progressing in this country not because of science or medicine but because of politics. This translated into fear on the part of the scientific community, cowardice on the part of industry, and at bottom a fundamental disregard for women and their

health needs.

The project over these past nine or 10 years has worked very hard to serve as a bridge between scientists and women's advocates, health care providers, practitioners, policy-makers and others to bring many voices and viewpoints to all of the deliberations, all the questions of safety, all of the questions about whether a product like this could really be adapted practically and safely in our health system in this country which is very different from the European system. We have taken on many, many, many of the questions that have been brought up today. I think that, as many people have said already before me, this kind of process that we have been through has given people the comfort and security that it is time, it is well past time that this product should be made available to American Women.

We believe that it is very important that you consider this drug in the same way that you would other drugs. We think you are doing that. We also think that it is very important that you not delay and not be subjected to any special considerations because of the politics of abortion. We remind ourselves that abortion is a legal medical procedure in this country that some women choose. As long as that is true, any potential new method should be considered in the context of medicine and a woman's good

health and not politics. So we depend on you to evaluate this product with the same careful, strict standards we know you will and move very quickly. Thank you.

DR. CORFMAN: The next speaker is Dr. Wendy Simonds speaking as a private citizen.

Agenda Item: Private Citizen Wendy Simonds, Ph.D.

DR. SIMONDS: Good afternoon, Chairman and members of the Advisory Panel. I am Wendy Simonds, a sociology professor at Georgia State University. The Population Council paid for my trip today.

One of my academic specialties is women's health. For the past six years my research has focused on abortion. I recently completed an ethnography of an abortion clinic which was published as a book entitled Abortion At Work this year. Over the course of my research, I spent a great deal of time talking with health care workers and the women they serve. My work leads me to believe that mifepristone will change the face of abortion in the United States. I am delighted that we have reached the point in this country where the FDA can consider approving mifepristone.

I would like to offer two points in support of this approval. First, it is my professional opinion that women seeking to terminate unwanted pregnancies will perceive mifepristone as a completely new option, wholly

different from surgical abortion. Many women who use mifepristone feel that they are active participants in their own abortions as others have testified. The provider gives a woman the pills, but she feels that it is her body does the work. Such an internal locus of control is healthy and helps women feel they are taking charge of a situation that may be upsetting.

Mifepristone abortion is less frightening to many women than surgical abortion because it involves no surgical instruments. It is far less invasive and affords women more dignity than surgical abortion does.

As others have testified, mifepristone would enable women to have abortions earlier than we could if surgical abortion were the only option. Unlike most other methods of abortion, mifepristone can work as early in the pregnancy as a woman wants. There is no need to wait once an unwanted pregnancy has been confirmed.

Secondly, my research has convinced me that mifepristone offers an entirely new option to abortion providers and other medical professionals.

In the field of abortion major technological breakthroughs have been rare and providers are keen to share this new choice with their clients. Mifepristone will also help doctors and their clients to avoid the harassment and terrorist tactics of anti-abortionists

because it allows more privacy. It can be offered in a variety of medical settings, not only in abortion clinics.

Many health care providers who do not now provide abortion would be willing to offer this new method.

In short, I believe mifepristone offers a ground-breaking and welcome abortion method to women and health care providers with important sociological implications for the United States. I urge the FDA to approve the drug swiftly if it deems it safe and effective. Thank you.

DR. CORFMAN: The next speaker is Dr. Seymour Romney, speaking for the Society of Physicians for Reproductive Choice and Health.

Agenda Item: Society of Physicians for Reproductive Choice and Health - Seymour L. Romney, M.D.

DR. ROMNEY: I am Dr. Seymour Romney. I am Professor Emeritus and the former Chair of OB-GYN at the Albert Einstein College of Medicine and have spent more than 45 years between comprehensive experience in Boston and New York in obstetrics and gynecology. I have seen a lot of things that we have talked about before and after Roe v. Wade.

The Society is an organization of physicians. They are a mixture of all disciplines. We are very much concerned about reproductive health care and the freedom of

inquiry in American medicine.

The Society urges the FDA to promptly approve this application. The clinical benefits of mifepristone should be made pharmacologically available to the American public as an established safe and effective drug. Our organization has an ethical and moral responsibility to ensure that everyone has the knowledge, access to quality services and freedom of choice to make their own reproductive health care decisions. We believe that every pregnancy should be an intended, wanted pregnancy.

Concerning mifepristone within the patient-doctor relationship, the medical profession has the ultimate responsibility to determine its safety and effectiveness. We have seen the informed consent form employed in the Population Council's clinical trials. It is accurately detailed and readily understood by any women seeking a noninvasive pharmacologic termination of early pregnancy. That is her constitutional right.

For physicians the exclusion clinical criteria in mifepristone protocols is the need to carefully evaluate whether patients are heavy smokers or have any evidence of heart disease, ectopic pregnancy, chronic liver or kidney disease that could complicate her care.

The Society of Physicians for Choice supports approving mifepristone. It is actually based on the

extensive clinical reports of safety and effectiveness in more than or approximately 200,000 women in France, Sweden, and Great Britain, as well as promising preliminary data concerning the therapeutic value of mifepristone in a spectrum of gynecologic problems including missed menses, term and post-term labor induction, endometriosis, fibroids, and very significant promise of therapeutic benefits obtained by mifepristone's inhibiting progesterone receptor activity in patients with breast and endometrial cancer, meningiomas, and other antiglucocorticoid conditions.

In further support of the application, and to additionally document the safety and effectiveness of this mifepristone application, the Society of Physicians for Choice respectfully requests that this detailed document, which is a report by the Institute of Medicine of the National Academy of Sciences published in April of 1993 entitled "Clinical Applications of Mifepristone, RU 486, and Other Antiprogestins," again, I would point to this document which is a public instrument be included as an important reference of this hearing.

This is a comprehensive report of a committee having expertise in cell biology, pharmacology, epidemiology, or reproductive endocrinology and care of women with hormone-dependent clinical conditions. It is an

unbiased evaluation of the science and the therapeutic potential of antiprogestins for numerous diseases and recommends clinical studies to further document the value of mifepristone.

The Society of Physicians for Choice believes that your committee has a commitment to the freedom of scientific inquiry and to the FDA and that the FDA in turn has a responsibility to the American public to approve the application that will permit mifepristone to be manufactured, distributed, and made available for indicated therapeutic purposes because of the overwhelmingly credible objective data that establishes it as a safe and effective drug.

In conclusion, I just wanted to say how pleased I was that Cynthia Person was able to introduce into your discussions the fact that mifepristone has a half life which is very short. In all of the discussions about the long-term complications that might come out of mifepristone's administration half life takes care of that problem.

DR. CORFMAN: The next speaker is Dr. Donna Harrison of the Southwestern Medical Clinic.

Agenda Item: Southwestern Medical Clinic - Donna J. Harrison, M.D.

DR. HARRISON: Dr. Davidson and members of the

Advisory Panel, good afternoon. I am Dr. Donna Harrison. I am a board-certified obstetrician-gynecologist in private practice in Michigan. I have been invited here by National Right to Life. I have no financial interest in RU 486.

As a physician and as a woman I am concerned about the premature approval of RU 486 without requiring normal safety and efficacy testing. I have followed the RU 486 approval process for several years. Along with many other physicians, scientists, and members of Congress, I participated in the citizens' petition filed with the Food and Drug Administration last year.

This petition summarized the world's literature on RU 486 and clearly outlines the following main concerns: Number one, the up to 10 percent hemorrhage rate necessitating hospitalizations and emergency surgery, of which 1 percent will be severe enough to require blood transfusion. If only one-third of the 1.5 million abortions annually in the U.S. are converted to chemical abortions, that would still result in 5,000 American women hospitalized each year for hemorrhaging, 500 of these each year massive enough to require blood transfusion. This excess morbidity is completely unnecessary in light of the already available surgical abortion which has a fraction of this risk.

Number two, the 5 to 10 percent rate of pelvic

infection requiring antibiotic treatment after chemical abortion with one World Health Organization study showing infection in a third of the women with incomplete abortions. In the U.S. if only one-third of the mean abortions annually were chemical, this would mean 25,000 American women with pelvic infections each year and a dramatic increase in subsequent sterility.

Number three, the 1 to 4 percent continuing pregnancy rate. There is also additional risk of severely deformed fetuses if the woman does not complete the entire procedure. In the U.S. experience documents poor compliance with 13 to 30 percent of surgical abortion patients failing to show for follow-up. In terms of RU 486 in real American women, this would mean 650 to 6,000 undetected pregnancies each year from failed RU 486 abortions. Who is going to assume the liability and cost of caring for these deformed children?

Note that the best results are from the French experience conducted under very tight governmental control with use only at or less than seven weeks from the last menstrual period as documented by ultrasound.

The Population Council has set up the popular expectation that RU 486 will be available with minimal medical supervision. That irresponsible communication undermines the need for tight medical control and clearly

increases the risk of hemorrhage, infection, and undetected pregnancies in American women.

If we ignore the documented immediate risks, we are still left with the unknown and unstudied but predictable effects of RU 486 on other progesterone-sensitive tissues. Relying on six months of trials with follow-up of two weeks is inadequate to answer our concerns of the effects of RU 486 on the brain, the endocrine system, the breast, the ovary, and developing eggs and the immune system. All of these can be profoundly affected by progesterone and all of these contain progesterone receptors which could be bound by RU 486.

What of the pharmacokinetic data? What about the half life of RU 486 plus misoprostol? Where does RU 486 accumulate and with what effect? What is the combined effect of RU 486 and misoprostol? What is the effect of repeat usage. Note that 42 percent of abortions in the U.S. are repeat. Are we going to confine the use of RU 486 to once only? What are the effects of RU 486 with common medical problems. Testing and use has been confined to health women, but the Population Council has set up the popular expectation that this will be used by teenagers and women with poor access to medical care, many of whom are my patients. I deal with a 30 percent Medicaid population, and 20 percent of my patients have no private insurance.

These are women with poor access to medical care who do not get appropriate medical screening.

What are the reasons for the discrepant results in minority populations, for example, Asian women with increased risk of hemorrhage? That will be the effect of a progesterone-mediated depression of the immune system on a growing HIV-positive population and the effect of RU 486 on a woman's chances of acquiring HIV?

The American public and the medical community do trust you to critically and impartially review RU 486 alone and in combination as an abortifacient. As a physician and as a woman I would urge you to prevent American women from being used as guinea pigs to satisfy a particular political agenda. Thank you for considering and addressing these grave concerns.

DR. CORFMAN: The next speaker is Joanne Hustead, the Women's Legal Defense Fund.

Agenda Item: Women's Legal Defense Fund - Joanne L. Hustead

DR. HUSTEAD: Congratulations on making it through the afternoon. My name is Joanne Hustead. I am an attorney and the Deputy Director of the Women's Health Program at the Women's Legal Defense Fund. Established 25 years ago, the Women's Legal Defense Fund is a national nonprofit advocacy organization that works on behalf of

women and their families improving access to quality, affordable health care including full reproductive choice which is one of our key program areas. We appreciate the opportunity to present comments today. We have no financial interest in this product or any other conflict of interest that would have any bearing on our comments.

We urge the Advisory Committee to recommend approval of mifepristone as a means for the interruption of early pregnancy. The record on its safety and effectiveness is clear and compelling. It offers women an essential alternative to surgical abortion for which providers are increasingly scarce and simple access increasingly burdensome and traumatic. Moreover, it may have important applications in other areas as well.

This breakthrough drug has been trapped in a political debate that has nothing to do with science, with medicine or with the real needs of women and their families. We are asking you to set mifepristone free and to confirm the rational scientific basis of the American drug approval process.

This drug combination would give women an essential alternative to surgical abortion. A woman could actually choose between significantly different medically proven methods to find the approach that was most appropriate for her. Making this drug combination

available would expand and improve women's reproductive health options in unique ways. One notable feature which has been mentioned by other speakers is that it enables women to terminate a pregnancy earlier than is sometimes the case with surgical abortion. Because it could potentially be administered in any doctor's office, it could significantly ease some of the barriers that now impede women's access to abortion in this country.

A stunning 84 percent of counties in the U.S. have no abortion provider and the number of doctors trained to perform surgical abortion continues to decline. The medical education community's efforts to ensure that doctors are trained in providing abortion services have been stymied by Congress. Among trained doctors, disincentives to providing surgical abortion include threats to their personal safety and the safety of their families. Those opposed to women's constitutional right to choose are easily able to identify and target doctors who perform surgical abortions.

Although there will always be a need for providers of surgical abortion, training to induce abortion with mifepristone would be different and easier. It is reasonable to conclude that many doctors who do not now provide surgical abortion services would include this drug in their practices.

Women seeking surgical abortion services face not only the challenge of simply locating a provider but also the likelihood of aggressive public harassment and the threat of violence at reproductive health clinics and medical offices. Approving mifepristone would help allow a very private and personal decision to remain as one.

This is a medical milestone with broad-ranging implications for women's health and ultimately men's health as well. Unfortunately, politics have artificially limited treatment options for all Americans. Denying or further delaying access to such important medical advances puts American women and men at an unnecessary and potentially tragic disadvantage.

In closing, you heard overwhelming testimony today that this drug combination is safe and effective. It is an appropriate and urgently needed alternative for women. Let us not deny women this safe and significant option. We urge you to recommend its approval. The women of America deserve no less.

DR. DAVIDSON: Now, that concludes the open public hearing. On behalf of the Committee, I certainly would like to thank all of the presenters who provided comments, opinions, and data in the consideration of the issues today. I am especially grateful that the time limitations that were set out in the beginning were so well

respected and conformed to.

We will recess and reconvene in 15 minutes to continue the committee's deliberations.

[Brief recess.]

Agenda Item: Committee Discussion and Consideration of the Questions

DR. DAVIDSON: I want to do a couple of things before approaching the questions. The first has to do with resolving maybe this technical issue that has been raised about alcohol and smoking. First, my concern about alcohol was not that it was included as an exclusion in the clinical trials; but the patients were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day of misoprostol, and that that was not a consideration in the patient information or the labeling. There are also some instructions about avoiding aspirin or any of its derivatives, steroidal or nonsteroidal anti-inflammatory drugs, prostaglandin synthesis inhibiting drugs, enzyme inducing drugs, oxytocic or prostaglandin, other than the one in the protocol. These were outside of the exclusions but were advisories to the patient.

With regard to smoking -- and Dr. Robbins, I understand, is prepared to respond to this -- as listed in the protocol, 35 years of age and smoking seem to be

separate exclusions in the French studies. I understand that Dr. Robbins may have a response to that and some other comments before we go further into the discussion.

DR. ROBBINS: Thank you, Dr. Davidson. I would just like to clarify a couple of things about the inclusion/exclusion, as you have already alluded to. In both the U.S. trial as well as the two pivotal French trials, the exclusion criteria was a combination of the following. Women could not -- women were excluded if they were 35 years or older and they smoked more than 10 cigarettes a day. It was a combination of the two in both protocols from France as well as the U.S. In one of those protocols the English translation as we have provided it had two separate bullet points for smoking and for 35. That has caused some of the confusion from the first protocol. In both of them when you read them in French the way they are written in French it is the combination as in our U.S. combination 35 years or older or smoking 10 cigarettes or more a day. And --

[Laughter.]

The other thing I wanted to speak to was a question that came up and Dr. Rarick said that the sponsor might have something to say about it. When Dr. Bardin had presented the cases of serious adverse events, as we always do, we presented that from the entire group that we had out

to 63 days or less. However, of those 52 patients who were reported with the serious adverse events nine of those were 49 days or less of gestation -- so nine of the 52. Of those one of those of the four that had a transfusion was less than 49 days, and three of the 26 hospitalizations occurred in subjects that were less than 49 days just to give you that breakdown of the safety data.

Finally, the third point I would just like to clarify. The question came up about the issue of taking misoprostol specifically 36 to 48 hours later. As Dr. Spitz has said, from a pharmacokinetic point of view, that is the time when it is most sensitive. However, as the protocol states, you take mifepristone on day one and on day three you take the misoprostol. So you have the whole time on day three to take it. It is not strictly to the 48 hours in terms of the way the protocol as well as the labeling is stated. Thanks for letting us clear that up

DR. DAVIDSON: Okay. Does the committee have any questions?

DR. LEWIS: Actually, I would like to raise one question. We heard from one of the speakers, I guess it was Dr. Harrison about a World Health Organization study and some safety points that seemed to be different than what was found in the French pivotal study. I wonder if

anyone has those data for our review or summary?

DR. DAVIDSON: I do not know if this answers this question, but this will be one shot at it.

Dr. Paul Van Loek, from the World Health Organization, was invited here by the Food and Drug Administration -- by the Population Council, I am sorry. Thank you for correcting me on that. He, as I understand it, has had considerable experience with the international use of this drug. I would like to give him just a few minutes to provide some background in terms of his relationship to this drug experience and whether or not he has any particular comments that would be of benefit to the committee in view of some of the issues that have been raised today. If you could, if you could use the podium?

DR. VAN LOEK: Thank you very much for giving me the opportunity to talk. I am Paul Van Loek. I am the Associate Director of the Human Reproduction Program at the World Health Organization. This is a program that conducts research in reproductive health. It is a program that has been involved with research in mifepristone since 1982. We have conducted with this drug close to 50 different studies including several large multi-center trials on the use of this compound for induction of first trimester abortion, menstrual regulation, second trimester abortion, and cervical ripening. We have in these trials used different

prostaglandins. We have used different treatment regimens of mifepristone, and we have done, as we always do, conducted these trials in a variety of developed and developing country settings. I should say right at the beginning that in the course of this experience we did not find any difference in efficacy or safety between different population groups. There was a question raised about that earlier whether data from the European women might be applicable to the different minorities here in the United States or of American Women in general. Certainly from the experience of doing trials in five continents we would not expect such a difference to occur.

During the course of the proceedings I have been flipping to the final data analysis of a most recent study that we have conducted in WHO with a protocol that is very similar to the French studies in terms of the timing of the misoprostol and the dose of the misoprostol. It is remarkable how similar the findings are to the data from the French studies as well as the preliminary data form the U.S. trial.

For example, if we look at efficacy -- and I have data -- the way that we did it was that the women were enrolled in the trial depending on the delay after the expected menstrual period. So, if we look at women with a delay of up to two weeks that would basically correspond to

six weeks amenorrhea, the efficacy is 95.5 percent. Those between two and three weeks it is 93.2 percent. Similarly, in the case of serious side effects in this particular study, the incidence of emergency D&C because of heavy bleeding was 1.4 percent which puts it sort of half way between the one percent reported from France and the two percent from the U.S. experience. Similarly for blood transfusion. We find similar data as reported from France in the sense that the incidence is 0.2 percent. I was confused earlier when a mention was made that heavy bleeding occurred in 10 percent of the women. I do not quite understand how that was defined.

These are some of the main observations that I wanted to make, but I am open for any questions that the committee may have.

DR. DAVIDSON: Dr. Henderson?

DR. HENDERSON: In the WHO studies in developing countries, I gather that there really was not perceived by the investigators to be any problem with the three-visit requirement?

DR. VAN LOEK: No. And certainly that is the way that it is also being done now in China. China, of course, as you may know, or as I am sure you know, is the only developing country at the moment where the drug was being manufactured as well as being used on a wide scale in a

slightly different regimen and is being --

DR. HENDERSON: What is the regimen?

DR. VAN LOEK: There are two regimens being used. One is a single 200 milligram dose. The other regimen is repeated doses of 25 milligrams given at 12 hour intervals.

DR. HENDERSON: What happens with a single 200-milligram dose?

DR. VAN LOEK: The same efficacy.

DR. HENDERSON: And they do not get followed up for a second visit?

DR. VAN LOEK: Yes. Of course, they have the similar routine scheme of three visits because they also have to come back for their prostaglandin.

DR. HENDERSON: And they do come back? In the developing countries they come back for that?

DR. VAN LOEK: That does not seem to be a problem. It certainly has not been a problem in our studies either. But, of course, we are talking here about women who make the choice to have this particular approach to pregnancy termination. So they know beforehand that this is what is going to be required. I guess, if someone has a difficulty in coming back for a second visit to get prostaglandin in a follow-up visit, then they may not opt for this regimen.

DR. HENDERSON: Do you have any data on the

numbers that are lost to follow-up in developing countries?

DR. VAN LOEK: In general, but again, these are clinical trials so one should not consider these hard and fast data. In fact, it may be larger. But our follow-up rates or loss to follow-up rates rather have been less than two to three percent. Now, that means people not coming back for their visit number three. They generally come back for the prostaglandin.

The fact that they do not come back is generally taken that probably it was successful. It has been very different from center to center. In this particular trial, for example, two-thirds of the people who did not come back for follow-up came from two centers, Tunis, and the other one was Ho Chi Minh City.

DR. DAVIDSON: Dr. Lewis?

DR. LEWIS: Do you have any information about fetal effects in women who carried the pregnancy after failure?

DR. VAN LOEK: We have -- none of the women that we know carried the pregnancy to term. They all had their pregnancies terminated.

DR. DAVIDSON: Thank you very much.

DR. KOSASA: I have one question.

DR. DAVIDSON: Oh, I am sorry.

DR. KOSASA: We had heard about pelvic

inflammatory disease with the WHO studies. Could you comment on that?

DR. VAN LOEK: I do not quite exactly know which study was being referred to. My recollection of what was said was that 30 percent of women with incomplete abortion had pelvic inflammatory disease. Now that is a slight twist I think of what the actual paper may have said in the sense that, first of all, incomplete abortions will only represent two or three percent of the women in total. So 30 percent of those two or three percent is less than one percent. Without exactly knowing the paper my guess is from our experience that women who have an incomplete abortion and if there is some suggestion that maybe there is a degree of endometritis, they may get antibiotics perhaps just as a primary prevention. In fact I am quite sure that these were not confirmed clinical pelvic inflammatory diseases.

DR. DAVIDSON: Did I miss anybody else's question?

DR. NARRIGAN: I would like to ask for your overall view of this regimen. Do you think the benefits from the World Health Organization's perspective, outweigh the risks or problems?

DR. VAN LOEK: As I am sure you are aware, there are about 50 million abortions in the world. Twenty

million of those are done under unsafe conditions. Our most recent estimates indicate that about 85,000 women die as a result of unsafe abortions, and 50 -- all of those are in developing countries.

There are a number of large developing countries where abortion is being provided on fairly broad liberal ground so to speak. The two that spring to mind are China and India. Together they account, of course, for something like 2.2 billion people. Both of these countries, China less than India, have some difficulty in providing safe surgical abortion services partly because of the need to have skilled people able to do it. If you can have a method that will remove some of the strain on surgical abortion services that would be an advantage. We saw this -- we mean the World Health Organization -- we saw this method as a potential benefit in those circumstances. That is why the World Health Organization became involved in studies of this kind. Clearly, these two countries themselves have taken the decision that this is indeed something that will be of benefit to them because China is producing it and using it and India I understand is about to start producing it as well.

DR. O'SULLIVAN: I have one last question. Knowing full well how studies are conducted in terms of follow-up and so on, can you tell me if in the studies

conducted by the World Health Organization there were efforts to get patients back in to make sure that they came in or whether they are just given the medication with an appointment to come back in and relied upon to come back in?

DR. VAN LOEK: No. Generally speaking in all of our studies, if people do not turn up for the follow-up visit, then the staff will go out and try to find them. With abortion it is sometimes a bit difficult because, for all sorts of social reasons, people may not always live at the address that they give to the staff.

DR. O'SULLIVAN: Oh, yes. We know that.

DR. DAVIDSON: Any other questions?

[No response.]

Thank you.

Before addressing the questions, do any of the members of the committee have any other general questions, concerns or observations to make before?

DR. AZZIZ: I have a question that maybe somebody from the Population Council can answer. It may be obtuse. We are really essentially considering a regimen not just a single drug at this particular point, which is a little unusual. The recommendation right now is 48 hours later for the delivery of misoprostol. The question is what if that drug were delivered four days later or five days

later? Would it be totally ineffective? Do we have any data in that regard? The reason I am asking that is most of the side effects of this regimen, if not all of them, are really related to the prostaglandin which is not being under consideration for approval and not to the mifepristone which is. So perhaps somebody from the Population Council could answer that.

DR. BARDIN: That is an important question because, as you already heard, the effectiveness or the synergism between the two drugs begins to be lost beginning about 48 hours after the first drug, the mifepristone. The protocol that was done in the U.S. study said that the patients should receive the dose on the third day, which is the second visit, anytime during that day. It allowed the clinician, however, to administer the drug if the patient did not come back but they came back the next day or the next. That allowed the physician the option to administer the drug that day if the patient came in because any number of things could delay the patient coming in. So we will have the opportunity in the U.S. study to examine that possibility. So that will be available to the FDA and to the prescribing physicians.

DR. DAVIDSON: Someone for the agency might be able to clear this up. My understanding, however, would be that we would have to stick to the recommended protocol.

Are there any other general -- yes?

DR. HENDERSON: I am very concerned that we are considering this regimen for a highly-selected and motivated population. I asked earlier in the U.S. study, the clinical trials, was there any demographic information we could look at understanding that the analysis is not completed, but at least to give a sense as to at some point in the near future we would be able to look at the breakdown of the patients who were being followed who have received this regimen?

DR. DAVIDSON: Is that a question, a comment or a hope?

DR. HENDERSON: Well, it was a comment of a question that I had asked earlier.

DR. DAVIDSON: Sure.

DR. HENDERSON: I was told that we could see the demographic data with the understanding that it is not analyzed but just to see the racial, the economic breakdown of the patients who were in the U.S. trial. I was told that was available.

DR. WINIKOFF: One of the issues is that the drug is so effective that there is very little difference between any subgroups that we have looked at. It is extremely effective in all of the subgroups. But, if you look at it, we have approximately one-third non-Caucasian

patients. The effectiveness -- what?

DR. HENDERSON: But the non-Caucasian -- there are Asian, there are Hispanics, there are African-Americans.

DR. WINIKOFF: They are all represented. I do not remember, but the proportions are approximately equal, but they are not far from that. They are all represented. As a result, no one group is very large. They are a little less than a third of the total.

DR. HENDERSON: So that is about a thousand patients who were divided in many ethnic groups?

DR. WINIKOFF: Yes. But some people claim more than one ethnicity, also.

DR. HENDERSON: Okay.

DR. WINIKOFF: We have a really diverse population. Even with 2,000 people you do not get very big cells if you start dividing it up a lot. We certainly have to give it --

DR. HENDERSON: And insurance coverage or socioeconomic status?

DR. WINIKOFF: The only indicator of socioeconomic status was payment. We have a small subgroup that only covered their medical care with Medicaid payment, but that was under a hundred patients.

DR. HENDERSON: And adolescents?

DR. WINIKOFF: No one under 18 was admitted to the trial because of informed consent issues.

DR. O'SULLIVAN: How about totally non-paying ingredients -- non-insured, non-paying?

DR. WINIKOFF: There were non-insured. There were some non-insured.

DR. O'SULLIVAN: What approximately?

DR. WINIKOFF: They are listed as self-pay because we do not know whether they could afford to self-pay or they could not afford to self-pay. But if they needed to pay they would have to self-pay.

DR. O'SULLIVAN: Well, what I am talking about is to make it very easy. Illegal aliens, migrant workers, that group of patients that --

DR. WINIKOFF: We did not, as far as we know, did not have any illegal aliens, but we did not ask people whether they were illegal aliens.

DR. O'SULLIVAN: So you do not know?

DR. WINIKOFF: Of course we also have age and parity issues which are part of the demographic profile that you might want to look at. The geography is spread out across the United States. So in terms of representation by region we have that as well.

DR. HENDERSON: Well, actually, I am not so concerned about age and parity. I am concerned about

patients who cannot afford -- access. That is what I am really interested in.

DR. WINIKOFF: In terms of the effectiveness of the drug?

DR. HENDERSON: No. In terms of following up for three visits, and ethnic issues, access to care, transportation, child care issues that will prevent them from being followed up for the second and third visit. That is what I am interested in.

DR. DAVIDSON: Does it help if they know up-front that those visits are required?

DR. HENDERSON: I do not think so. Because I think if women desperately want it then they will figure out that they will do something when they are faced with that issue. But right now they want the drug. What happens when they cannot show up for the second and third visit or when they cannot afford to have the termination because it has failed, the surgical procedure? I mean, what do we do with those populations of adolescents, of minority women who are already lacking access to pregnancy termination?

DR. DAVIDSON: Let me ask -- I understand. What general assurance do you have in listing patients for these protocols that they will follow through with any scenario whether it is surgical termination or otherwise?

DR. WINIKOFF: Let me say something first about studies in general. The most important thing in the study is to find out whether the drug is safe and effective. So our highest priority is to get complete records on all patients. So, in that sense, you may say that the situation is somewhat artificial, irrespective of ethnicity. Dr. Van Loek mentioned that in the WHO studies people go out to find patients because it is extremely important to know what happened. What we found out is that with complete follow-up there are very few patients who need extra care or who do not complete the abortion. So we are at least assured that problematic outcomes are relatively rare.

Now, how the drug operates when it is offered in real life as it were is always different and it always needs to be looked at after it is offered in real life. You cannot get answers to real life questions in study circumstances. So I think that your concern is valid but it is one that needs to be addressed as a product is used and as it is available. It cannot be addressed in a study situation. But we have some reassurance because we have such a safe and effective drug.

DR. O'SULLIVAN: I think you have to address one part of it, and that is that, if this were to be approved, then what is going to have to be looked at somehow or

another and dealt with is what do you do for the patient who completes her course but cannot afford the surgical termination. How do you follow-up a patient or patients who start out the therapy and, for reasons which women will change their minds about many things in life, suddenly decide it did not work to quote what I often here, this was God's will, I am going to keep on with the pregnancy? How do we follow those up? I mean, this is probably post-marketing surveillance. But I think that it is essential that if we were to approve this that post-marketing surveillance of this type has to be done.

DR. WINIKOFF: I agree that we in all medical care have issues like this. There is no reason to suppose that the surgical abortion would not be part of the package the way the cesarian is part of the package of obstetrical care. If you run into a complication that requires a more complicated delivery, it is part of the service. If you run into a complication that requires a curettage, it is part of the service. So surgical patients also need reaspiration sometimes and they also get it as part of the service. So I think that these things are medical care issues that our system is already dealing with. I agree that they are very important.

I think a lot of the issues are not so far into providers of abortion. Surgical abortion patients also

sometimes cannot afford care and run into complications and need to come back at a later point. And the system has accommodated that and can continue to accommodate that. It obviously is something --

DR. DAVIDSON: Dr. Daling?

DR. NEWHALL: May I respond to that? I just have a couple of issues. The women that we generally serve in our downtown women's center clinic generally are of lower economic status. Women with good health insurance much more often will avail themselves of services in a private offices. So we already serve the lower socioeconomic women primarily.

Number two, as Beverly said, the price includes whatever surgical back-up is necessary. You pay one price, and you end your pregnancy. I think that it is important to remember that women are motivated to have a complete, and safe, and effective abortion. They come to us because they want to have their pregnancies terminated. They are motivated to complete the process and they are motivated to have their health care adequately protected. We put Laminaria in women for surgical abortion and they always come back. We have a very high follow-up rate in our clinic. Women are interested in preserving their good health. They do come back. Now, there are occasional circumstances when they cannot. They call up, they say how

they are doing, and they come back at a later time. But the women who did this trial with us understood that there were two drugs that worked together and that the first step happened on Monday, and the second step happened on Wednesday, and it was not a one-stop shopping -- that they absolutely needed to come back Wednesday or there was absolutely no guarantee that their abortion would be in effect. So all of the women came back for the second visit and there were very few who did not come back for the third visit. In fact, what we did was we saw a lot of women four, five, and six times just because we were all in the learning process. We encouraged women to come back more often rather than less often. We saw a lot of our women. I am very comfortable that they all received good, adequate health care and were very comfortable coming back as often as they needed to for the questions they had and the service that they needed.

DR. DALING: In this trial did the women pay for their abortions?

DR. ROBBINS: No, they did not.

DR. DALING: Were they given financial compensation?

DR. ROBBINS: No.

DR. DALING: I heard this morning -- I asked the question about follow-up and I heard that there was a

hundred percent follow-up for all three visits. And I spoke to you a little while ago and you said, well, that was not true that for the third visit you had three women who did not return. You just had 172 in your group or something to that effect. I guess that I am a little concerned that these numbers -- the hundred percent follow-up is not really an accurate figure.

DR. NEWHALL: There were some women who I think did not actually physically come back to the clinic but they were contacted by phone and they were not bleeding, and they had had nonviable pregnancies before they left, so it was not really a question of -- there were no ongoing pregnancies or any ongoing health problems.

DR. DAVIDSON: Dr. Zones, did you have a question?

DR. ZONES: It was just answered.

DR. DAVIDSON: Oh, okay. These are important questions, however, in bits and pieces we are drifting into some questions that are already on our list. So, if the committee is comfortable, why don't we start with the questions? Are there any objections to that?

[No response.]

Agenda Item: Discussion and Response to Questions

DR. DAVIDSON: Let's read the first one. The

regimen proposed for the use of mifepristone for the termination of early pregnancy consists of the oral administration of 600 milligrams of mifepristone within 49 days after the beginning of the last menstrual period, followed by oral administration of 400 micrograms of misoprostol 48 hours later.

I have one question about that 48 hours that I would like to ask both the agency or the Population Council. All of the clinical data in general relates to a window of 36 to 48 hours rather than this specific 48 hours. Is this an issue that should be modified now or should it be left as it is?

DR. RARICK: Are you proposing to say 36 to 48 hours or are you proposing to say two days? Which one are you talking about?

DR. DAVIDSON: I am asking -- that is the nature of my question. Since you have specifically 48 hours --

DR. RARICK: No. We say the regimen proposed. And that is draft labeling proposed by the Population Council. If you feel that we need to recommend a different 36 to 48 or two days, as it is stated in the patient labeling, we could certainly take that under advisement and you could change that section to what you are comfortable with.

DR. DAVIDSON: Well, let me ask, in regards to

two days versus 36 to 48 hours, people who are familiar with the trials, is that -- which one of those would be more accurate in terms of what is clinically being requested?

DR. ROBBINS: Two days.

DR. DAVIDSON: Two days. And that falls within the window of effectiveness and synergy that is true?

PARTICIPANT: Two days later.

DR. DAVIDSON: What is your question?

DR. RARICK: I think that is what the patient labeling says, anyway. So I am sure you are comfortable with that.

DR. DAVIDSON: Okay. So we are changing this to two days. Is that acceptable to the committee?

PARTICIPANT: That is better.

DR. DAVIDSON: That is better I hear. Okay. All right. I think that we will have less problems if it is stated that way. So you understand the proposed regimen and it has been modified so that the misoprostol will be administered two days later rather than 48 hours.

Question 1A. Do the results of the open label historically controlled studies conducted in France establish the efficacy of this regimen for use in the United States? Any discussion or questions on question one?

[No response.]

Are you ready to vote on question one without any further discussion?

DR. O'SULLIVAN: No.

[Laughter.]

I am just thinking about it. I think that I would like to say that with a caveat that it would have been preferable to have U.S. data. In fact, we are talking about the fact that everybody is quoting that this has been used in 150,000 women throughout the world and yet the data presented is something like one to two percent who were ever studied at least that we have data on and that data is not even American data.

DR. DAVIDSON: But the question restricts this in a way that you can either respond or object to. The question limits it to the French.

DR. O'SULLIVAN: Okay.

DR. DAVIDSON: Any further discussion of this question?

[No response.]

Do the results of the open label historically-controlled studies conducted in France establish the efficacy of this regimen for use in the United States? Are there any further questions?

[No response.]

Let's take the voting members. All in favor of that statement, raise your hands.

PARTICIPANT: You mean yes to that statement?

DR. DAVIDSON: Yes. Yes to that statement, raise your hand.

[Show of hands.]

One, two, three, four, five, six.

Opposed?

[Show of hands.]

Six to two. Yes, I have counted myself.

PARTICIPANT: So it is six to two?

DR. DAVIDSON: Yes. If not, what additional efficacy information should the applicant provide? Yes?

DR. HENDERSON: I think a less-selective patient population. These are highly-motivated women who were selected and had their terminations paid for by the clinical trials. I think that it should be women who are much more likely to avail themselves of the services in the states.

DR. DAVIDSON: I am going to --

PARTICIPANT: I am going to use the formal minority report and put it on the table so that --

DR. DAVIDSON: Well, let me tell you -- let me explain where I think I am here. The committee by a majority vote supports the first question that the French

data is sufficient for efficacy. The second was an if not question; but since there were two people objecting what I am hoping to provide at least for the record as to what those objections are. So it would be helpful if you would clarify if that fits into this scheme here what those objections or further conditions should be in regard to the French data.

DR. O'SULLIVAN: In regards to the French data?

DR. DAVIDSON: Well, that is what the question is.

DR. O'SULLIVAN: What additional efficacy?

DR. DAVIDSON: Yes.

DR. O'SULLIVAN: It does not say that it has to be from the French data.

DR. DAVIDSON: Well, either way you would like to respond.

DR. O'SULLIVAN: I would like to see the final American data. I agree with Cassandra that it is very much of a study situation. I think it would be wise if we could see what would happen in what I would call the main stream of Americans who would be going to do this I think like she did.

DR. DAVIDSON: I am sure that both of you -- just a comment -- are familiar with the fact that study populations are always somewhat special and that

translation from that to a non --

DR. HENDERSON: Yes, but the patients who were not going to come back are a patient population that is very, very different. If necessary, then they need to be studied separately in a separate study. I commend the Population Council for bringing this to the FDA. I think it is a very valuable tool for taking care of women and increasing reproductive rights and options, but I also believe that there is a great risk for harming a very large, vulnerable population if we do not study them and make sure that once this is available that they are not irreparably harmed.

DR. DAVIDSON: Is that sufficient?

DR. O'SULLIVAN: I agree.

DR. DAVIDSON: Those are two points. Yes?

DR. AZZIZ: I am not a voting member right now. I just wanted to add a comment.

DR. DAVIDSON: But you have no restrictions to speak.

DR. AZZIZ: And I will take that. I have the same concerns as far as requiring -- I am not as concerned about the population data. I mean, populations that are noncompliant will be noncompliant with everything from surgical terminations to ectopic precautions. But I am concerned that in a fairly sensitive environment that we

are in we do not have the complete U.S. efficacy data which is promptly available but not today. I would like to make a comment that perhaps for this type of situation that would be very ideal.

DR. DAVIDSON: Would it be acceptable to advise the agency that when the U.S. data is available, if there is any significant difference than the French data that we would at least like to have an opportunity to review that? Would that be an unreasonable -- I understand what you are saying because, if the U.S. data comes in and there is essentially no significant difference in any respect than at least to the point that data is available to answer that question it would be reviewed. And, if there are differences, then since the committee has been invited to advice up to this point, then perhaps we would be interested in seeing it. What does the committee feel about that?

DR. LEWIS: Agreed.

DR. HENDERSON: I am off the committee.

[Laughter.]

DR. DAVIDSON: The committee is an institution that goes on.

[Laughter.]

DR. HENDERSON: Okay.

DR. DAVIDSON: So whatever the concern is it is a

committee concern that is institutionalized. All right.

The committee -- you may want to -- the committee has reservations about final efficacy questions without the U.S. data and recommends to the agency that if this data when completed is significantly different than the French data that the committee would like an opportunity to review it. All in favor of that, raise your hand.

[There was a show of hands and the motion was approved unanimously.]

That is unanimous.

DR. NARRIGAN: Mr. Chairman? You mean worse than? If it is better than, it is moot.

[Laughter.]

If it is better than --

DR. DAVIDSON: Do you want -- what would you -- if it is worse than? Is that acceptable, if it is worse than? Okay. Thank you very much. Worse than. We might want to see it if it is better.

PARTICIPANT: Yes.

DR. DAVIDSON: Okay. Is that all right?

PARTICIPANT: Sure.

DR. DAVIDSON: The second question. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience. A, do these data adequately

demonstrate that the regimen is safe for use in the United States when use for the proposed indication? I do not think -- okay, Dr. Sullivan?

DR. O'SULLIVAN: What foreign postmarketing experience did we see?

DR. PETITTI: This was a question that I asked actually Dr. Rarick about the postmarketing surveillance experience and adverse stress experience from the British Committee on Safety of Medicines and other drug regulatory agencies, and I was reassured by her that that information had been reviewed and that it did not present an adverse event profile different from what we saw from the trials from France and the United States. Is that a correct summary of your and Dr. Bennett's summaries?

DR. RARICK: What I said was that the Population Council had submitted a report about post-marketing surveillance to their I&D and asked them if they wanted to comment on it. In my recollection there was not anything of startling or unexpected findings in that report.

DR. PETITTI: We did hear comments on cases of acute myocardial infarction and other kinds of adverse cardiovascular events associated with the regimen of mifepristone and misoprostol, and it was my understanding that that was part of the international adverse drug experience. Am I correct?

DR. RARICK: Correct.

DR. DAVIDSON: Okay. Do you have all of the information available that you would like? Let me read it again. The safety database for the regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience. Questions. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? In your discussion please include comments on the following issues whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled, the acceptability of the frequency of adverse events? Any discussion on this question? Yes?

DR. PETITTI: I would like to comment that safety is a relative term and that although this may be safe for this indication, I think that some of the information that I have seen in the popular press and some of the rhetoric surrounding this regimen and this drug leads people to think that safe is equivalent to free of adverse effects. I am impressed in the data that have been presented here that although the frequency of adverse effects is low that there is a significant and important number and frequency of adverse effects and that this needs to be carefully understood by the consumer and by providers who might seek

to deliver this service. So I want to worry that the term safe not be misinterpreted as free of adverse effects and free of actually serious adverse effects.

DR. DAVIDSON: Good. But then are you remarking in the vein that that is a labeling and a patient information leaflet problem?

DR. PETITTI: But an important one.

DR. DAVIDSON: Yes. Okay. All right.

DR. DALING: Ezra, I would like to see some collection of multiple procedures for an individual women, I mean, not in regard to our decision here, but I think that that is something that information needs to be collected on.

DR. DAVIDSON: Could that be done in number 7?

DR. DALING: Yes.

PARTICIPANT: Number 7.

DR. DAVIDSON: Okay. Then we have a rich opportunity to raise all of those kinds of questions. Okay. Let's read it again and see where we are and how you feel about it. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials and foreign post-marketing experience. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? You have discussed the adverse emphasis and

how that needs to be taken as a high and clear priority in terms of labeling and patient information leaflet. Are you ready to answer that question? Any unreadiness?

[No response.]

All in favor or who support that raise your hands.

[Show of hands.]

Seven.

Any opposition? Abstention?

DR. O'SULLIVAN: Abstain.

PARTICIPANT: She is abstaining.

DR. DAVIDSON: Abstain. Seven for and one abstention.

Would the second bullet, the acceptability of frequency of adverse events, do you have anymore to say about that other than points that may ultimately be raised as labeling or patient information leaflets?

DR. LEWIS: I think acceptability should be perhaps looked at compared to what, compared to other methods of pregnancy termination, compared to carrying a pregnancy? Acceptable depends on -- it is a relative term. I think that it should be couched as such.

DR. DAVIDSON: Is it -- this is a question to the staff, to the agency -- is it possible, or are there data -- I guess we do have data on alternative --

DR. KESSLER: One way to think about that question is what a rational person and a rational physician talking together, knowing all of the adverse events both known and unknown would be acceptable -- would that risk be acceptable for a rational person? Would they want knowing those adverse events to possibly avail themselves of the drug? That is a way to think about that.

DR. DAVIDSON: Okay.

DR. LEWIS: Well, it is not so much the way of thinking about it I suppose as a way of answering the question or -- I mean, to just say flat out yes sounds a little ridiculous because it is not that simple a question. But I think if you say, well, it compares favorably with surgical methods of pregnancy termination then that seems to be --

DR. KESSLER: It certainly is another way to answer that question.

DR. LEWIS: Something like that.

DR. DAVIDSON: So your interest would be to the extent that it is possible --

DR. LEWIS: Uh-huh.

DR. DAVIDSON: -- that the method be compared with alternatives in terms of adverse effects and events?

DR. LEWIS: Yes.

DR. DAVIDSON: And you would like to include that

as a comment to the agency in the labeling to the extent that that is possible?

DR. LEWIS: Yes.

DR. DAVIDSON: I think that is a very good point and may be very helpful in terms of perspective.

DR. LEWIS: Yes.

DR. DAVIDSON: Since you have answered A in the affirmative, I guess there is no necessity for B if not, but I will give you an opportunity anyway, knowing this --

DR. LEWIS: We are never at a loss for words.

DR. DAVIDSON: Dr. Azziz?

DR. AZZIZ: I will take the opportunity again to echo the same thing. I would like to see the finalized U.S. data on safety. In fact, I am not sure that I would favor it being sent only if it is different. I would rather I think have it sent --

DR. DAVIDSON: You mean only if it is worse.

DR. AZZIZ: But no, in this case, I think that the safety issue should be reviewed when it is finalized period as opposed to --

DR. O'SULLIVAN: Better or worse?

DR. AZZIZ: Better or worse.

DR. O'SULLIVAN: For richer or poorer.

DR. AZZIZ: That is right. I would appreciate seeing the data either way is what I guess I am saying.

That is my comment.

DR. DAVIDSON: Well, we could change the -- we originally said that and then we modified it to be worse.

DR. AZZIZ: I am not sure. There are only eight committee members. I think it perhaps would not be that much of a task to send the data anyway once it is finished regardless of what -- because you see it is a very subjective issue as to whether it is worse or better than France. It will not be identical. So I think that the members may find it useful to get that data.

DR. DAVIDSON: Do you want to comment on that -- interpret that movement?

DR. RARICK: I said, no, I do not want to comment.

[Laughter.]

But, no, but I think we have heard you that you are very interested in seeing the results of the U.S. study probably either way. You are simply very -- you are appropriately curious as to the final result.

DR. CORFMAN: I think it would be good for the committee to know whether we are likely to bring data back too.

DR. RARICK: As a group in a public setting?

DR. CORFMAN: Uh-huh.

DR. RARICK: I think we would have to think about

that depending on the results. If they are the same or better they may get to receive them simply in the mail with an opportunity to comment. If they are appreciably worse, then maybe they will -- I cannot really answer that question.

DR. DAVIDSON: Okay. All right.

Are we ready to go to three? Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe that the benefits outweigh the risks for the use of the regimen for the proposed indication in the United States?

DR. O'SULLIVAN: Can I ask a question?

DR. DAVIDSON: Sure.

DR. O'SULLIVAN: Benefit to whom?

DR. DAVIDSON: Do you want to answer that question?

DR. RARICK: The regimen is proposed for use for a woman for the termination of pregnancy for a woman to take.

DR. O'SULLIVAN: Because, if you are talking about a woman, it may be a benefit to her, but it is certainly of no benefit to her baby whatsoever.

DR. DAVIDSON: Well, the benefit is to the woman.

DR. RARICK: It is proposed to be taken by the woman to terminate the pregnancy.

DR. DAVIDSON: Okay. Let's read it again to make sure. Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States which is to complete an abortion?

DR. HENDERSON: I would like to add to it a select population of well-motivated, highly-motivated women. I think that you cannot -- I cannot comment on the whole population across all socioeconomic statuses and the availability of access to health care. I think that is a very limiting part of our society.

DR. DAVIDSON: Well, are you saying that it should read informed and well-motivated or other than that? You want to add informed and well-motivated?

DR. HENDERSON: Yes. That may be difficult. Just leave it and I will just add my comment. You can leave it.

DR. DAVIDSON: Leave it as it is or do you want it modified?

DR. HENDERSON: No. I will just comment. Leave it.

DR. DAVIDSON: Any other comments? Are there any other comments as to how this question is worded?

DR. O'SULLIVAN: I want to know what the exact

wording of this is going to be.

DR. DAVIDSON: We will do that.

DR. NARRIGAN: I just wanted to respond to Cassandra's concerns. I am much more reassured having heard even informal comments from the WHO representative concerning it seems to me the safety in very, very complex situations. It is not the United States I understand.

DR. HENDERSON: The WHO went and got patients, and they went and visited them. They called them if they did not come. Most of the women that I am concerned about, no one is going to go and get them. No one is going to call them because a lot of them do not have phones. Those are the women that I am concerned about.

DR. LEWIS: That is always the case in a clinical trial though. I mean, anybody conducting a clinical trial has a responsibility to follow up with their patients.

DR. HENDERSON: Right. That is why I --

DR. LEWIS: And you are not going to get data until after it is approved in a non-ideal population. I just think that it is not going to happen.

DR. DAVIDSON: We are generating a fair amount of response to this.

DR. DALING: Maybe we can work on this in question seven, post-labeling surveillance.

DR. LEWIS: You could qualify it.

DR. DAVIDSON: Would that satisfy you? Look at seven?

DR. HENDERSON: I looked at seven. It is postmarketing.

DR. DAVIDSON: I mean, would your concerns be accommodated if there were appropriate conditions raised in regard to question seven?

DR. HENDERSON: I will think about that.

DR. DAVIDSON: Okay. Dr. Zones?

DR. ZONES: I have a couple of thoughts. One is that this is an additional option for women seeking to terminate pregnancy. Therefore, they can weigh the cost and benefits of each of the methods and which was best for them through the advice of their physician. But also it seems to me that there are other medical procedures where we face the same difficulty. The one that comes to my mind is cervical dysplasia where, if the physician thinks that the woman will not continue to seek care, they will do a much more invasive procedure than if they think the person is likely to come back. It seems to me in this situation that physicians or providers will have to make judgments about what is the most appropriate procedure in consultation with the patient.

DR. DAVIDSON: Yes.

DR. DALING: One other comment. A lot of these

studies were carried out in Planned Parenthood. I think that they see a population, a broad population, and one -- a population that has a high concentration of the type of people whom I think Cassandra is concerned about.

DR. DAVIDSON: Any further comments? Did you have one?

DR. AZZIZ: No. Actually, that exactly was my point. I think that it is true that there is some bias because they have been paid to come back.

PARTICIPANT: Well, they are not paid.

[Discussion off record.]

DR. AZZIZ: Well, let me rephrase that. Their expenses have been covered. Okay. Wait a minute.

PARTICIPANT: Free care? They are provided free care?

DR. AZZIZ: Weren't there termination --

PARTICIPANT: Their procedures were paid for.

DR. AZZIZ: The procedure was paid for.

PARTICIPANT: It was free.

DR. AZZIZ: Well, let's not get into semantics. The procedure -- let me just finish a comment here.

PARTICIPANT: They had access.

DR. AZZIZ: There is some bias because obviously these people were highly sought for and their termination expenses were covered; however, I just simply wanted to

echo the fact that most of these patients were actually indigent patients who do attend planned parenthood and other clinics and, thus, represent a more difficult sector of the population. So I am not quite sure that I agree with Dr. Henderson's comments that this represents a significant bias.

DR. DAVIDSON: As a generic observation though in clinical research regardless of what the issue is, there is always a concern that once you move from clinical trials which has a selective focus on it, what is going to be the compliance and other questions when it is put in general?

DR. HENDERSON: I understand that. The thing that concerns me is that at the second visit, if they do not show up, what happens? They then come back with a pregnancy that has not been aborted that has been exposed to a new medication? It is not just simply that they are different, but the consequences are so dire that they may have a fetus that they are forced with having to decide to terminate because they have been exposed to this medication. They may be coerced into having a suction because they delayed the prostaglandin. I understand that all clinical trials when you put them into practice are going to be different.

I just think the consequences of this particular trial if women do not follow-up are so severe that it just

requires extra caution besides just knowing that it is going to be different in practice. Because I think that the potential for coercion, the potential for adverse perinatal outcome I think is great. I just think that that needs to be addressed because it is not just simply putting a clinical trial. If it was one drug and they did not show up and you deal with the consequences, that is fine; but there are two drugs, and you need to confirm that the pregnancy has been avoided. And there are all kinds of consequences -- there is a mechanism that just sets off a cascade that if they do not follow through is so severe that I think it is different than just any clinical trial.

DR. KOSASA: Dr. Davidson? We have kind of run into the same problem with Laminaria. We put a Laminaria in and then if the patient does not come back we get quite nervous and try to find them.

DR. HENDERSON: I understand. But then you do not have -- you have this concern that maybe she is going to have a preterm delivery. You have the concern that maybe she is going to have an infection. But you then do not have the concern that she carries a fetus that may have some malformations. And while we have the data that suggests that it is highly unlikely, if she does, it will be highly unlikely and difficult to prove that it was not something that we did and gave it to her. I think it is

very different. I mean, I agree with you. Laminaria is a problem when you send patients home and ask them to come back. But I think the consequences are so vastly different that it concerns me.

DR. DAVIDSON: We have been told by some of the people who are working with the populations that include at least some patients in the category that you are concerned about that compliance seems to be reasonable. I guess that is not enough to satisfy what your reservations are. However, do you accept -- this is really a question -- that some of your concern and reservation is also hypothetical?

DR. HENDERSON: Absolutely.

DR. DAVIDSON: Okay. Let's read the question again and see where we are.

Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States? Is there any further discussion or comment on readiness about voting on that question?

[No response.]

If not, may we vote?

If yes, raise your hands.

[Show of hands.]

That is six, am I right?

PARTICIPANT: Are you voting?

DR. DAVIDSON: Yes, I am voting. Raise your hands. Six. All right.

Opposed?

[Show of hands.]

Abstentions?

[Show of hands.]

Six yes, two abstentions.

PARTICIPANT: No, one -- which are you doing the voting no or abstaining?

The voting, yes.

PARTICIPANT: Let's do it again, please.

PARTICIPANT: I am sorry.

DR. DAVIDSON: Okay. All yes, raise your hands.

[Show of hands.]

One, two, three, four, five six. There are two abstentions.

PARTICIPANT: I thought it was seven.

DR. DAVIDSON: No. Only eight people voted.

PARTICIPANT: Why don't you let us finish, Cindy?

PARTICIPANT: It is six.

DR. DAVIDSON: It is six.

PARTICIPANT: Six. And how many are against?

DR. DAVIDSON: Two abstentions.

PARTICIPANT: Two abstentions. Thank you.

PARTICIPANT: Who is voting?

PARTICIPANT: Deborah and Mary Jo.

DR. DAVIDSON: There are eight votes.

PARTICIPANT: I think it is a generic question as to who is voting at this table.

DR. RARICK: The voting members include Dr. Daling, Dr. Henderson --

DR. DAVIDSON: There are eight voting members.

DR. RARICK: -- Dr. Petitti, Dr. Davidson, Dr. O'Sullivan, Dr. Narrigan, Dr. Lewis, and Dr. Kosasa. There are eight.

DR. DAVIDSON: Right. Okay? Next question. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients to receive it to be appropriate?

DR. DALING: I think they need to add to the labeling that the studies done to date do not apply to women who are over 35 and are smokers or smoke more than 10 cigarettes per day since the data was not collected on those people.

DR. RARICK: Do you have any specific concerns about that age group or smoking-specific concerns that you think they are at higher risk for some reason? I just wanted to --

DR. DALING: They may be. I mean, they certainly must have been thought to be because they were eliminated from this study to begin with.

DR. DAVIDSON: The group that was eliminated, if I understand this, are the ones who are over 35 and smoke?

DR. DALING: That is right.

DR. DAVIDSON: That is what you are saying?

DR. DALING: That is what I am saying.

DR. DAVIDSON: Over 35 and smoke. And what is your question now?

DR. RARICK: Some of the medical conditions such as prior cardiovascular disease were not included in the proposed labeling, yet again they were eliminated from the studies.

DR. DALING: They were included in the provider labeling but not in the patient labeling.

DR. ZONES: Were there contraindications?

DR. DAVIDSON: Your interest is that the conditions that were excluded in the trial should also be identified as exclusions in the patient -- at least that the trials did not include patients with those conditions?

DR. DALING: That is right. Just that information. We do not --

DR. DAVIDSON: Just provide that information.

DR. DALING: We cannot really address that issue.