



UNDP/UNFPA/WHO/WORLD BANK  
Special Programme of Research, Development and  
Research Training in Human Reproduction (HRP)

# Impact of HRP research in medical (non-surgical) induced abortion: a case-study

Reviewer

**Jane Norman**

Regius Professor of Obstetrics and Gynaecology,  
University of Glasgow, Glasgow, Scotland

With assistance from

**William Winfrey**

Futures Institute, Glastonbury, CT, USA  
for the economic analysis



**World Health  
Organization**

**UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP).  
External evaluation 2003–2007; Impact of HRP research in medical (non-surgical) induced abortion: a case-study.**

© World Health Organization 2008

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: [bookorders@who.int](mailto:bookorders@who.int)). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: [permissions@who.int](mailto:permissions@who.int)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Views expressed in this document are those of the 2003–2007 HRP External Evaluation Team.

Printed in Switzerland

# Contents

Executive summary	1
Introduction	3
Methods	3
Rationale	4
Process	5
Contributions of other stakeholders	7
Inputs	7
Outputs	8
Future	16
References	18
Annex 1. Full text of paragraph 8.25 of the Programme of Action of the International Conference on Population and Development	20
Annex 2. Clinical trials on medical abortion	21
Annex 3. Strategic reviews	26
Annex 4. Selected publications from HRP during the review period	28
Annex 5. Percentage of medical abortions among all abortions in selected countries, 2006	31
Annex 6. Countries and year of approval of mifepristone	32
Annex 7. Countries of approval of misoprostol	33
Annex 8. Economic costs of medical abortion	34
Annex 9. Annual estimates of potential unsafe abortions and maternal deaths averted in countries where mifepristone is registered or likely to be registered	36



# Executive summary

Unsafe abortion, defined as “a procedure for terminating an unintended pregnancy carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal standards, or both”, remains a major public health problem. Medical abortion, that is abortion effected by drugs rather than a surgical procedure, is a safe and effective alternative to surgical abortion and can potentially play a major role in reducing unsafe abortion.

## Methods

This review was conducted on the basis of face-to-face meetings with HRP personnel and other stakeholders and by a review of the published literature on medical abortion from WHO and other sources. The focus of the review was activities between 1997 and 2007.

## Findings

HRP's work on preventing unsafe abortion included highlighting the issue; conducting, analysing and publishing clinical trials on medical abortion; preparing guidelines; and collaborating on promoting the use of Medabon®. HRP's direct expenditure on research on medical abortion was US\$ 1.7 million over the eight-year period 1999–2007.

The outputs fall into three categories: an extensive, widely cited list of original publications; registration of Medabon®; and addition of mifepristone and misoprostol to the *WHO model list of essential medicines*. Other outputs include contributions to meta-analyses and systematic reviews, organization of sessions at conferences, conduct of local and regional workshops, generation of new research questions, and individual and institutional capacity-building.

HRP worked with 15 medical centres and three academic institutions in conducting its clinical trials

and in public–private partnership with the (not-for-profit) Concept Foundation and the pharmaceutical firm Sun Pharma in the registration and production of Medabon®.

### *Cost-effectiveness (including finances)*

The price of Medabon® is significantly lower than both the public and private sector prices of its components, mifepristone and misoprostol. Estimation of the numbers of women worldwide who could access Medabon® at its anticipated cost, but who could not afford mifepristone marketed by current manufacturers and who would otherwise choose unsafe (surgical) abortion, indicates that 1 million unsafe abortions and 3600 maternal deaths could be averted annually by registration of Medabon® where abortion is legal. HRP expenditure on medical abortion over the past eight years could be translated into a projected cost of US\$ 0.95 per unsafe abortion averted and US\$ 264 per maternal death averted.

### *Outcomes and global public goods*

Most of HRP's work in medical abortion during the decade (1997–2007) involved conducting clinical trials. Five of the seven large randomized clinical trials conducted in developing countries in the past 10 years were undertaken by HRP. These trials are of the highest quality, have clear relevance for clinical service provision and were conducted with sufficient rigour and detail that they can be used to support licensing applications for mifepristone and misoprostol. This is unusual for academic clinical trials, and HRP deserves to be congratulated for having achieved this degree of quality. HRP-run clinical trials have been cited (which is a quality indicator) twice as often as the two large trials conducted by other organizations in developing countries during this period.





Additionally, HRP has disseminated the results of these trials in evidence-based clinical guidelines and reports. They have also, in strategic reviews of abortion provision generally, helped governments to develop strategies for introducing medical abortion.

HRP also collaborated with the Concept Foundation to enable the manufacture, registration and distribution of a low-cost, good-clinical-practice standard medical abortion product (Medabon®) to the public sector in developing countries. This ambitious and novel approach has enabled translation of HRP clinical research into a formulation that can benefit developing countries.

## Impact

HRP's work has contributed to changing the global health status, with a demonstrated 5.4% reduction in maternal mortality between 1990 and 2005, and work on preventing unsafe abortion is likely to effect further reductions. The rate of unsafe abortions per 1000 women of reproductive age has also declined.

There has been a significant increase in access to medical abortion: Medabon® is now registered in one country, and registration is pending in a further 10 countries. The work of HRP on misoprostol allows health-care providers to recommend a safe regimen (albeit less effective than the mifepristone–misoprostol combination) in countries where mifepristone is unavailable. Where medical abortion with mifepristone is legally available, about 50% of women chose this option for inducing abortion.

## Conclusions

### *Successes and failures*

The major success of HRP's work in this area is the good clinical practice standard clinical trials, which

have provided an important knowledge base for medical abortion practice and enabled registration of a low-cost formulation. The strengths of these trials include collaboration between HRP and research centres and individuals, which allowed these trials to be completed as planned within a small budget. The work done by HRP during the period is highly cost-effective and is likely to have a major impact in reducing unsafe abortion.

There are no apparent failures or major weaknesses of HRP's work in this area. Funding shortfalls have necessarily limited the scope of activity.

### *Lessons learnt*

Timely publication is crucial in translating HRP's work into practice. The excellent data from the clinical trials must now be matched by research on how to introduce Medabon® into countries where abortion is legal.

## Recommendations

- HRP should sustain its influential, evidence-based, highly respected leadership in facilitating safe medical abortion, replacing unsafe practices.
- WHO, other cosponsors and members of the Policy and Coordination Committee should help the new Director of HRP to maintain HRP's work in prevention of unsafe abortion.
- Now that much of the work has been done to define an appropriate regimen, future work should focus on barriers to service delivery and on synthesis of evidence.
- The WHO management hierarchy should review its internal procedures for approving publication of work on abortion, including medical abortion, and set targets to minimize the delays.

# Introduction

HRP has been active in the field of medical abortion since the early 1980s. The most recent review of HRP's activities in this area was performed in 2003, when Management Sciences for Health and the Swiss Centre for International Health

jointly reviewed HRP's programme. The present review was commissioned in 2007, with the aim of evaluating how, by investing in HRP, the world has changed in terms of medical abortion.



# Methods

- Meetings with personnel in HRP (Helena von Hertzen, Peter Fajans, Ronald Johnson, Iqbal Shah, Craig Lissner and Jane Cottingham) to map the scope of HRP's activities (especially clinical trials, interaction with governments, nongovernmental organizations, commercial companies, patient groups and advocacy).
- A literature search in Medline to identify published clinical trials; assessments made of quality, impact (including impact factor) and contribution to knowledge generally.
- Review of HRP's web site to determine other activities related to medical abortion (e.g. publications, guidelines, policy initiatives and activities mentioned in newsletters).
- Review of a synthesis of the evidence on medical abortion from the *WHO Reproductive Health Library*.
- Internet search on Google to identify other references.
- Information from HRP personnel on unpublished activities, e.g. presentations at conferences, training workshops, interactions with governments and nongovernmental organizations, and advocacy.
- Review of trends in use of medical abortion worldwide (where possible), abortion-related deaths, access to medical abortion and access to abortion itself during the period under study.
- Review of other articles on medical abortion (review articles and editorials) for background information against which HRP's work was conducted and to determine the impact of HRP's activity.
- Review of web sites and publications of other groups in this area [e.g. Gynuity Health Projects, William and Flora Hewlett Foundation ([www.id21.org](http://www.id21.org)), the postabortion care consortium ([www.pac-consortium.org](http://www.pac-consortium.org)), Guttmacher Institute] to establish their activities and elicit comments on HRP's activity in medical abortion during this period.
- Interviews with other players: Khama Rogo, Beverly Winikoff and Peter Hall.
- Teleconferences with Douglas Huber and William Winfrey.

# Rationale



Unsafe abortion, defined by WHO (WHO, 1992) as “a procedure for terminating an unintended pregnancy carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal standards, or both”, remains a major public health problem. It is estimated that in developing countries, one woman dies every eight minutes due to the complications of an unsafe abortion, and the procedure accounts for around 13% of maternal deaths (WHO, 2007a). Detailed modelling of abortion-related maternal deaths suggests that medical methods might have a major impact in reducing mortality related to unsafe abortion, especially in developing countries (Harper et al., 2007).

The stated aims and responsibilities of WHO are to provide leadership on global health matters, shape the health research agenda, set norms and standards, articulate evidence-based policy options, provide technical support to countries and monitor and assess health trends. Provision of medical abortion (where abortion is legal), to prevent unsafe abortion, is entirely consistent with these aims and is mandated by paragraph 8.25 of the Programme of Action of the International Conference on Population and Development (ICPD, Cairo, 1994) (Annex 1). The mandate was reinforced in 1999 at the five-year review of the ICPD Programme of Action by the United Nations General Assembly.

Specifically, the role of HRP in the area of medical abortion is to:

- assist countries, on request, to identify and set priorities on needs related to preventing unsafe abortion and strengthening sexual and reproductive health services, design and implement research to address the priorities, and scale-up successful policy and programme innovations;
- provide guidance on the management of complications of unsafe abortion;
- find safe alternative approaches to pregnancy termination; and
- formulate evidence-based technical and policy guidance on safe abortion.

The comparative advantage of HRP over other groups in its work in medical abortion was outlined in some detail during the previous review. The breadth, capacity, prestige and credibility of HRP, with its international composition and links with national governments, was highlighted, and its international leadership in the area of unsafe abortion was emphasized (External Evaluation 1990–2002, available at [www.who.int/reproductive-health/management/index\\_hrp.html](http://www.who.int/reproductive-health/management/index_hrp.html)).

Unsafe abortion, like many health problems, disproportionately affects women in low-income and developing countries. The incidence is eight times higher than in developed countries (16 compared with two per 1000 women of reproductive age), with the highest rates in least-developed countries (25 per 1000 women of reproductive age) (WHO, 2007). One thousand-fold more deaths occur in developing countries than in developed countries due to unsafe abortion.

Global public goods were defined by the Independent Evaluation Group of the World Bank as those goods that “produce benefits that are non-rival (many people can consume, use or enjoy the good at the same time) and non-excludable (it is difficult to prevent people who do not pay for the good from consuming it)”. Much of the work of HRP in medical abortion contributes to knowledge on medical abortion methods, and it assists countries in providing medical abortion, either by strategic evaluation of the infrastructure required or by providing low-cost formulations through the public sector. Thus, HRP’s work on this topic fulfils the criteria for global public goods.



## Process

HRP has done much to highlight the issue of unsafe abortion, including publications on its incidence and its contribution to maternal mortality (Ahman, Shah, 2004; Grimes et al., 2006; Khan et al., 2006; Warriner, Shah, 2006; Sedgh et al., 2007a; WHO, 2007). Given that, “In circumstances in which abortion is not against the law, [such] abortion should be safe”, finding safe abortion methods is an important part of any strategy to reduce unsafe abortion. This case-study focuses on medical abortion, although other safe techniques, such as manual vacuum aspiration, can be used in appropriate settings. Recent HRP studies have shown that this method can be used safely by mid-level providers, who might also be able to perform medical abortion where access to doctors is limited. Given that no method of medical abortion is 100% effective, it is implicit in this case-study (and explicit in HRP publications) that medical abortion services should include access to surgical uterine evacuation for the small (< 5%) proportion of women who require it.

During the period under review (1997–2007), HRP conducted and published the results of eight randomized trials on medical abortion methods, focusing on areas of relevance for prevention of unsafe abortion globally (Tang et al., 1999; World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation, 2000, 2001a, 2001b; Tang et al., 2002; von Hertzen et al., 2003; Honkanen et al., 2004; von Hertzen et al., 2007). Both the combination of mifepristone–misoprostol and misoprostol alone were studied. Most of these trials were carried out in developing countries, complied with good clinical practice and provided a crucial evidence base for medical abortion protocols (see Annex 2 for details). The rigour and detail with which these trials were conducted meant that the results could be used for licensing applications. This was particularly

important for registration of Medabon®, the low-cost mifepristone–misoprostol formulation being promoted by the Concept Foundation (see below). It is unusual for academic (i.e. not conducted by the pharmaceutical industry) clinical trials to meet this required standard; industry trials normally have much greater resources at their disposal to enable them to achieve it. The studies of misoprostol alone demonstrated that this is the most effective regimen when mifepristone is not available.

HRP formulated guidelines for medical abortion during the period of the review (1997–2007), which are based on the results of the clinical trials. Additionally, HRP has ensured that the guidelines affect practice through dissemination, meetings and interactions with governments, made possible by WHO, with its respected profile. Two guidelines published during the review period are:

*Medical methods for termination of pregnancy—report of a WHO scientific group, 1997* ([http://whqlibdoc.who.int/trs/WHO\\_TRS\\_871.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_871.pdf)):

This report is a consensus statement by leading scientists, which, although published by WHO, was accompanied by a statement that it did not necessarily represent WHO policy decisions. It included a review of medical methods for termination of first- and second-trimester pregnancies, including studies on agents that induce abortion, their mode of action and their efficacy in comparison with surgical methods.

*Frequently asked clinical questions about medical abortion* ([http://www.who.int/reproductive-health/publications/medical\\_abortion/index.html](http://www.who.int/reproductive-health/publications/medical_abortion/index.html)):

This document was the result of deliberations of participants at an international consensus conference on medical abortion organized by HRP in 2004, who included highly experienced researchers and clinicians.





Additionally, in the field of safe abortion generally, HRP published *Safe abortion: technical and policy guidance for health systems, 2003* ([http://www.who.int/reproductive-health/publications/safe\\_abortion/safe\\_abortion.pdf](http://www.who.int/reproductive-health/publications/safe_abortion/safe_abortion.pdf)). This book gives norms, standards and advice for Member States to help them strengthen the capacity of their health systems to manage complications of unsafe abortion and provide high-quality abortion and family planning services as part of an overall package for improving maternal health.

In order to facilitate access to the drugs used for medical abortion, HRP has focused in recent years on collaboration with the Concept Foundation in developing a prepackaged preparation of mifepristone and misoprostol, Medabon®. The Concept Foundation (<http://www.conceptfoundation.org>) is a not-for-profit organization the aim of which is to ensure access to medicines in developing countries by manufacturing pharmaceutical products that comply with the standards of good manufacturing practice.

It had become clear from work conducted by HRP and others that the limited availability of mifepristone (because of lack of licensing and registration) and therefore its price were barriers to the wider use of medical abortion. With this in mind, a Framework Agreement and a Licensing Agreement were established between HRP and the Concept Foundation in 2004–2005 ([http://www.who.int/reproductive-health/publications/annual\\_technical\\_reports/2005/text.pdf](http://www.who.int/reproductive-health/publications/annual_technical_reports/2005/text.pdf)) to facilitate the manufacture, registration and distribution of mifepristone for medical abortion. Sun Pharma, an Indian pharmaceutical company, was identified as a manufacturing partner, and, together, Sun Pharma and the Concept Foundation produced Medabon®. The preparation consists of 200 mg

mifepristone (one tablet), to be taken on day 1, and 0.8 mg misoprostol (four tablets) to be taken on day 2 or day 3. Data (published and unpublished) from WHO clinical trials will be used for registration of the regimen with drug regulatory agencies in developed and less developed countries. An agreement with Sun Pharma and national governments that will import the product will make the mifepristone–misoprostol combination available at a preferential price for purchase by the public sector in developing countries where the regimen is registered.

The introduction of safe medical abortion requires much more than registration and marketing of drugs in the relevant country. HRP has been instrumental in initiating a strategic approach, in which the current provision and potential methods for improving that provision are explored, before recommendations to introduce a new technology are made. An overview of potential strategies is outlined by WHO (2003). During the period of assessment, strategic assessments were performed in Ghana, Moldova, Mongolia, Romania and Viet Nam (Annex 3).

In addition to these strategic reviews, HRP undertook a study of the safety and efficacy of abortions conducted by mid-level providers in South Africa and Viet Nam. Although the manual vacuum aspiration was used, the conclusion of the study, that there were no discernable or significant differences in the rates of overall or major complications in first-trimester abortions performed by mid-level providers and by physicians, is potentially relevant (*Annual Technical Report 2004*, available at [http://www.who.int/reproductive-health/publications/annual\\_technical\\_reports/2004/text.pdf](http://www.who.int/reproductive-health/publications/annual_technical_reports/2004/text.pdf)).

# Contributions of other stakeholders

Interest in medical abortion is not limited to HRP, and many other organizations, including Gynuity Health Projects and Ipas, are also involved, particularly with the developing world. HRP works with many of these agencies to reduce the burden of unsafe abortion; however, its strategy is unique, as it involves both research to improve the safety, efficacy and acceptability of methods of abortion and post-abortion care and also strengthening national health system management and support systems to ensure the availability of high-quality, sustainable, safe abortion and post-abortion care

in accordance with national laws and relevant international conventions and agreements (<http://www.who.int/reproductive-health/hrp/progress/73.pdf>). HRP is the only internationally cosponsored programme and the only instrument in the United Nations system and internationally that addresses unsafe abortion in a scientific, systematic, integrated manner. Additionally, respect for and the profile of WHO mean that HRP can make a major impact at the level of governments, which is often crucial for success in preventing unsafe abortion.



## Inputs

During the eight-year period 2000–2007, the HRP expenditures for sexual and reproductive health projects exceeded US\$ 96 million, with project expenditures of US\$ 1.7 million on medical abortion.

HRP's work in this field has been conducted in partnership with many individuals, institutions and governments, which HRP acknowledges and values. Collaborating centres in a variety

of locations are involved in this work, including Beijing, Chandigarh, Helsinki, Ho Chi Minh City, Hong Kong, Ljubljana, Mumbai, New Delhi, Oslo, Shanghai, Singapore, Stockholm, Szeged, Targu Mures and Ulaanbaatar. The universities of Aberdeen, Edinburgh and Stockholm, which have been involved in medical abortion techniques since the mid-1980s, have maintained their interest in, and support for, this work.

# Outputs



Publications, electronic and print, and presentations at conferences are listed in Annex 4. The HRP team also organized and participated in many conferences and sessions on abortion. For example, HRP organized a session on induced abortion at the XXV International Population Conference of the International Union for the Scientific Study of Population, France, 2005. HRP also participated in an international conference on policies, programmes and services related to medical abortion, organized by the International Consortium for Medical Abortion, with which HRP collaborates. Over 100 delegates attended the international conference. The availability and cost of mifepristone and misoprostol were highlighted as a major stumbling block to expanding the introduction of medical abortion.

HRP also organized local and regional training workshops for good clinical practice. Three were organized for Eastern European investigators, in May 2005, October 2006 and September 2007, in Szeged, Hungary. HRP also gave training in good clinical practice to investigators participating in the five most recent multicentre trials, launched between 2002 and 2006.

A workshop was held in June 2004 in Riga, Latvia, which was attended by participants from Latvia, Lithuania, Moldova, the Russian Federation and the Ukraine. Strategic assessments, similar to that conducted in Moldova (Annex 3) are being planned for the Russian Federation and the Ukraine. In 2005, in collaboration with the WHO Regional Office for South-East Asia and Ipas, HRP organized a workshop on reducing unsafe abortion in Asia, which was attended by representatives of governments, professional organizations, researchers and nongovernmental organizations from Bangladesh, Bhutan, Cambodia, India, Indonesia, Maldives, Mongolia, Myanmar, Nepal,

Philippines, Sri Lanka, Thailand and Viet Nam. The WHO publication *Safe abortion: technical and policy guidance for health systems* (WHO, 2003), which provides details of appropriate medical abortion regimens and services, was used as a basis for preparation of action plans.

In 2007, a regional workshop on unsafe abortion for Anglophone African countries was organized by Ipas with technical and financial input from HRP. The workshop involved country teams from Malawi, Nigeria, Uganda and Zambia, which worked on plans of action for a strategic assessment of services to prevent unsafe abortion, on the basis of the HRP strategic approach and the WHO guidance document. Medical abortion will be one of the key service delivery issues discussed during the assessments, to be carried out during the 2008–2009 biennium.

In November 2007, an HRP staff member facilitated a one-day training workshop for a country team in Macedonia planning to conduct a strategic assessment on issues related to abortion. The assessment will focus on strengthening the abortion law and related policies and programmes, including possible introduction of medical abortion, in preparation for European Union accession talks in 2008.

Some e-learning on evidence for medical abortion is provided through the *WHO Reproductive Health Library*. Training in medical abortion is not part of the HRP mandate and is undertaken by other organizations, such as Ipas.

HRP experts contributed to a systematic review of medical methods for first-trimester medical abortion (Kulier et al., 2004). This confirmed that 200 mg mifepristone is as effective as 600 mg, paving the way for use of the lower dose in the Medabon® formulation, thus minimizing its

cost. The greater efficacy of vaginal over oral misoprostol and of the combined mifepristone–prostaglandin regimen compared with either given alone were important conclusions from this systematic review, as was the need for more research in developing countries.

HRP experts contributed to a systematic review of medical and surgical abortion, initially published in 2002 (Say et al., 2002) and updated in 2005 (Say et al., 2005). The efficacy of the two regimens was compared, but it was considered that there was insufficient evidence to compare the acceptability and the side-effects.

The size and quality of the clinical trials conducted by HRP in this area means they constitute much of the data reviewed in meta-analyses.

## Generation of new research questions

HRP generates new research questions through a variety of approaches. The most effective basis is detailed knowledge of abortion services (and lack of abortion services) throughout the developing world, available through strategic and collaborative links with abortion providers encountered while conducting randomized trials. Additionally, new research questions are identified by consensus groups at international meetings, which HRP has either organized or at which it makes presentations. Many of the new research questions are tested in randomized clinical trials, strategic analyses or cost–effectiveness analyses. Some are not pursued because of funding or personnel constraints (see below).

## *Individual and institutional capacity building*

The mission of the International Consortium on Medical Abortion, established in 2001 with input from HRP, is to increase access to safe abortion and promote choice of abortion methods by making medical abortion more widely available where it is legal.

There is good evidence that HRP activity in clinical trials on medical abortion is important in making health-care providers familiar with the techniques in a supported environment. Thus, medical abortion often continues to be provided (local laws and availability of drug permitting) after the conclusion of a clinical trial. Additionally, HRP clinical trials and training in good clinical practice are important in building capacity to conduct other clinical trials, in the field of sexual and reproductive health or other areas.

## Outcome: public goods

The major public goods arising as a result of HRP work in this area are the published clinical trials on medical abortion regimens, which make a significant contribution to the literature in this area, and work (with the Concept Foundation) on generating, licensing and enabling distribution of Medabon®.

## *Clinical trial literature*

The impact of HRP clinical trials is impressive and important. HRP published the results of eight clinical trials during the review period. Although this might appear to represent a small fraction of the 80 published trials in this area, not all the trials are of equal importance or impact. The 'best' trials, i.e. those that change clinical practice, are likely to be sufficiently large to provide a definitive answer to the question posed. Additionally, the citation index (the number of times the publication





is quoted in the literature) is likely to be high. Trials on medical abortion published during the relevant period had a wide range of sample sizes, from < 50 to over 2000. If a sample size of 1000 women or greater is taken as indicating a large study, then 20 such studies were published during the period of review, and HRP was responsible for five of those publications (World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation, 2000; World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation, 2001a; von Hertzen et al., 2003; Honkanen et al., 2004; von Hertzen et al., 2007). Thus, HRP is a major contributor to seminal studies on medical abortion, as assessed by study size or citation index. More detailed analysis reveals the unique contribution of HRP: of the 20 'large' trials, 11 were conducted in the USA and two in western Europe, and were thus potentially less relevant to women in the developing world. Of seven large studies of medical abortion in developing countries, five were conducted by HRP and two (Elul et al., 1999; Ngoc et al., 2004) by the Population Council.

The number of times each HRP trial had been cited as of November 2007 is as follows: World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2000): 43 citations; World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2001a): five citations; von Hertzen et al. (2003): 23 citations; Honkanen et al. (2004): 14 citations. The two major trials published by other organizations during this period (Elul et al., 1999; Ngoc et al., 2004) were cited seven and 13 times, respectively.

Thus, although the other two trials are valuable, it is clear that advances in medical abortion strategies and the evidence base for the strategies that are best in practice are largely confined to work by HRP. If one considers large studies (those

that are most likely to achieve their goals and most likely to reveal the 'truth' about side-effects and the efficacy of a strategy), it is clear that HRP contributes more than any other player in the field, much of the evidence base depending entirely on HRP studies. The importance of these studies and their relevance for achieving both the Millennium Development Goals (MDGs) and the stated aims of WHO is further underlined by the fact that most were conducted in developing countries, which have higher-than-average background rates of unsafe abortion. Thus, the relevance of these studies and their probable impact in preventing unsafe abortion in countries with the highest prevalence is likely to be high. They also made a major contribution to the guidelines described below.

### *Guidelines for improving quality of service delivery*

Guideline development is discussed in some detail above. The contribution of WHO has been, firstly, to generate data for the guidelines and, secondly, to convene conferences at which consensus could be achieved (e.g. the Bellagio conference, resulting in the publication of *Frequently asked clinical questions about medical abortion* (Geneva, WHO, 2006). These guidelines are among the few guidelines on medical abortion of relevance for developing countries. Although some countries had, by the time this booklet was published, produced their own guidelines (China, France and the United Kingdom), little other guidance was readily accessible and suitable for use by practitioners in developing countries. Other guidance available at the time of publication included the Gynuity Health Projects publication *Providing medical abortion in developing countries; an introductory guidebook* (Abuabara & Blum, 2004), which was the result of a meeting held in Bellagio in 2000.

National guidelines for medical abortion services (e.g. in Ghana, India, Mongolia, Romania, South Africa and Viet Nam) have been drafted by governments with assistance from HRP. HRP research results were used as the basis for the protocols.

### *Changes in policy and adoption of evidence-based practices*

There is evidence of substantial change in policies and practices in Mongolia, Romania and Viet Nam, among others. For example, in Mongolia, mifepristone and misoprostol have almost completely replaced intrauterine injections of ethacridine lactate for second-trimester abortion; however, use of mifepristone and misoprostol for first-trimester abortion in public sector facilities is still too expensive.

After HRP technical input to the 2005 workshop on reducing unsafe abortion in Asia (described above), teams from four of the 13 countries represented drew up proposals for follow-up activities, either for menstrual regulation (Bangladesh) or for the prevention of unsafe abortion (Nepal, Sri Lanka and Thailand). Introduction of medical abortion techniques also followed trials in e.g. India (personal communication, Professor Suneeta Mittal, Head, Department of Obstetrics and Gynaecology, All-India Institute of Medical Sciences, New Delhi, India), Sweden and the United Kingdom.

In Viet Nam, it is estimated that 6% (50 000) of abortions are now conducted medically (Annex 5).

### *Changes to WHO model list of essential medicines*

In 2005, the sequential medical abortion regimen of mifepristone and misoprostol was added to *WHO model list of essential medicines*. Such inclusion

requires a formally constituted independent expert committee to agree that the scientific data confirm that the medicines are safe and effective. This could not have been achieved without HRP's clinical trials in this area, again demonstrating the importance of this work.

### *Public good attributed to HRP's work*

It is impossible to be certain of the relative contributions of HRP and of other organizations to the global public good of medical abortion. It is clear, however, that HRP is the major player in both conducting and publishing clinical trials and in enabling Medabon® to be produced and licensed. Regarding the latter, Peter Hall (personal communication) said, "the fact that HRP ... did the clinical trials on mifepristone and misoprostol is the reason that we are now in the final phases of making a co-packaged product, Medabon®, available at an affordable cost to the public sector of developing countries. This is a great achievement which has been made through a collaborative agreement between WHO and the Concept Foundation."

## **Impact**

### *Health outcomes, improved health status*

There was a 5.4% reduction in maternal mortality between 1990 and 2005, and it seems likely that HRP's work contributed to this decrease (Shah, Say, 2007). The rate of unsafe abortions per 1000 women of reproductive age declined slightly between 1995 and 2003, but the proportion of all abortions that were unsafe increased slightly, from 44% to 48% during the same period (Sedgh et al., 2007b).

In relation to medical abortion specifically, there is increasing evidence (reviewed above) that illicit





use of medical abortion can reduce mortality and morbidity from abortion, especially in areas where unsafe abortion is prevalent due to restrictive legal policies.

### *Access to goods and services and numbers of people benefitting*

The work on mifepristone and misoprostol combinations and misoprostol alone has significantly increased knowledge about medical abortion. Access to mifepristone for medical abortion is growing but is still limited (Annex 6). Where mifepristone is registered, a significant proportion of women choose medical abortion (Annex 5). Women choosing this option may prefer medical abortion because it demedicalizes the process.

Misoprostol is more widely available (Annex 7), and work by HRP has been crucial in defining safe regimens for its use. This is likely to reduce recourse to unsafe methods in situations where women would otherwise have no alternative. Additionally, Medabon<sup>®</sup>, a good-clinical-practice standard, low-cost, mifepristone–misoprostol combination, is a major advance. HRP has been important in providing clinical trial data for registration of Medabon<sup>®</sup>.

### *Contribution to MDGs*

One of the major aims of HRP's work on unsafe abortion is to contribute to achieving MDG5: to reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio (<http://www.mdgmonitor.org/goal5.cfm>). Work by HRP shows that there was a modest, 5.4% reduction in the maternal mortality ratio between 1990 and 2005 (Shah, Say, 2007). At an annual change of 0.4% per year, progress at this rate will not achieve the MDG by 2015. Within this overall modest change,

however, some countries have changed their maternal mortality ratio considerably, and the role of safe abortion is evident in a number of these countries: for example, the maternal mortality ratio in Romania fell by 50% over a two-year period after liberalization of abortion laws (Hord et al., 1991). Nevertheless, it is clear that unsafe abortion remains a major contributor to maternal mortality, highlighting the need for further work in this area (Sedgh et al., 2007b).

A low-cost medical abortion product (Medabon<sup>®</sup>) can allow major savings, both to public health services and to individual consumers. Further details are included in the economic evaluation below.

### *Potentially harmful effects*

If used inappropriately outside a health service setting or without access to back-up services, medical abortion can result in complications, including bleeding and incomplete abortion. The HRP strategy has consistently been to provide information about potential adverse effects and to include strategies for their minimization in its guidelines.

## **Cost–effectiveness**

The following is an attempt to estimate the potential impact of improved access to medical abortion, which can result from registration of mifepristone, availability of adequate infrastructure or more affordable prices. Other factors for improving access to and use of medical abortion are not addressed here, including distribution of medical abortion, training of medical personnel and improved knowledge of its availability.

At the time of writing, mifepristone had been registered for medical abortion in 36 countries,



15 of which are in regions where unsafe abortion persists. The Center for Reproductive Rights, New York, NY, USA has categorized almost every country in the world according to the legal status of abortion (Center for Reproductive Rights, 2007): (1) the highest category is countries where there are no restrictions; (2) second is those where abortion is permitted on socioeconomic grounds; (3) third is countries where abortion can be performed to preserve mental health; (4) fourth is where abortion is permitted to preserve physical health; and (5) fifth is countries in which abortion is permitted only to save a woman's life, or is prohibited altogether. There is considerable variation within these categories, but they serve as good summary measures. Countries in categories 1, 2 or 3 might be good candidates for registration of mifepristone in the future. HRP has also indicated that a few countries in categories 4 and 5 might reform their abortion laws in the near future, including Ethiopia, Mozambique, Nigeria and Uruguay. Therefore, 42 additional countries might be good candidates in the future. The countries in which mifepristone is either registered or considered to be a good candidate for registration are included in the estimates below.

A second factor that might limit expansion of medical abortion, especially in the early phases of introduction, is access to appropriate medical personnel. In these estimates, the percentage of births attended by trained medical personnel is used as a proxy for the percentage of the population that would be covered by health-care personnel able to deliver medical abortion. This might be an overestimate or an underestimate, depending on local circumstances.

The third factor that might limit expansion of medical abortion is its cost. The commodity costs of medical abortion with the combined

mifepristone–misoprostol regimen are significantly higher than those associated with manual vacuum aspiration, dilatation and curettage or misoprostol alone. With support from HRP research, however, the recommended dosage of mifepristone has fallen. Subsequent to this research, HRP supported policy work and collaboration with the commercial sector that has or will result in a reduction in the commodity price for the recommended dosage, from US\$ 15 (the previous minimum import price for 200 mg) to US\$ 3.60 for the new recommended formulation of the mifepristone–misoprostol combination.

Even at the lower price, not all women in all countries who require abortion services will be able to afford them, or the health system will not be able to procure them. Countries are therefore grouped according to per capita income (World Development Indicators Online, accessed 5 December 2007, current US\$). In each group of countries, the percentage of the population able to pay for medical abortion is assumed to differ, depending on the price of mifepristone (all other costs are assumed constant for the purposes of this analysis). The percentage of the population that can pay is estimated by comparing one week's income evaluated at various points on an income distribution with the US\$ 3.60 price or the US\$ 15 price, and a representative income distribution was fitted to the midpoint income of each group of countries. (Details are available from the evaluation team.) Annex 8, Table 2 shows the percentages that were applied. At the lowest income, US\$ 0–500 annual income per capita, it is hypothesized that 5% could pay US\$ 15 and 50% could pay US\$ 3.60. These percentages increase as annual per capita income increases.





Annex 9 presents broad regional estimates of the potential numbers of averted deaths due to unsafe abortion in countries under four scenarios:

- **Scenario 1:** Mifepristone is free and fully available to all women; i.e., all unsafe abortions would be eliminated as well as attendant deaths.
- **Scenario 2:** Mifepristone is free and available to women with access to adequate medical personnel.
- **Scenario 3:** Mifepristone costs US\$ 3.60 and is available to women with access to adequate medical personnel.
- **Scenario 4:** Mifepristone costs US\$ 15 and is available to women with access to adequate medical personnel.

The four scenarios include only the countries in which mifepristone is registered or has a reasonable potential for being registered. The scenarios assume that if a pregnant woman is given a choice between medical abortion that is accessible and affordable or unsafe abortion in prevailing conditions and prices, she will choose medical abortion. The scenarios also assume that medical abortion is the only method of abortion that will become more accessible as regulatory inhibitions on abortion are relaxed. The prevalence of manual vacuum aspiration, a safe method of abortion, might also increase. These projections might overstate the potential impact of medical abortion. The estimates do not take into account the indirect impacts of improved services that will come with increased availability of medical abortion. For example, improved post-abortion care should result in greater post-abortion family planning, which, in turn, will lead to a decrease in the number of unintended pregnancies.

Estimates of the impact of price reduction in each of these scenarios are shown in Annex 8. (See

also Annex 9 for estimates of maternal deaths averted for each scenario, by region.) The impact is calculated as the difference between the scenario in which mifepristone costs US\$ 3.60 and that in which it costs US\$ 15. At the bottom of the table, as points of reference, are the levels of unsafe abortion and mortality in 2003.

Scenario 1 shows that some 9.1 million unsafe abortions and nearly 36 000 deaths could be averted in countries in which mifepristone has been registered or may be registered. Scenario 2 shows that, after correction for health system capacity, the number of unsafe abortions averted is about 4.8 million and the number of deaths averted is about 14 000. Correction for ability to pay further reduces the numbers of averted abortions and deaths. At a price of US\$ 3.60, it is estimated that 3.9 million unsafe abortions could be averted; at US\$ 15, 2.9 million abortions would be averted. The difference between these two figures is the net impact of a price reduction. About 1 million unsafe abortions and about 3600 deaths could be averted as a result of the price reduction.

HRP reported direct expenditure of US\$ 1 693 000 dollars on medical abortion activities over the past eight years. With salary overheads (about 36%), this amounts to US\$ 2 645 000. Over 10 years, with moderate expectations for achieving the price decrease shown in Annex 8, Table 2, these will translate into about US\$ 0.95 per abortion averted and US\$ 264 per death averted. At the end of 10 years, 50% of the potential impact of the price decrease will be assumed to have been achieved. For the intermediate years, the potential impact is interpolated between 0% and 50% (e.g. 5% in the first year, 10% in the second year, etc.) Deaths and abortions are not discounted, and annual pregnancies are assumed to be constant, for simplicity and to obtain conservative estimates.

### *Impact on poverty*

Michael Vlassoff (2006) demonstrated that the economic costs of unsafe abortions per woman are high. He estimated a global average of patient cost per hospital treatment for unsafe abortions of US\$ 238. He reported that, of 19 million unsafe abortions each year, about 9.7 million should be treated but only 5.7 million are actually treated. He also estimated an annual total US\$ 511 million of lost income due to seeking and receiving medical treatment. Annex 8, Table 1 extrapolates from the abortions averted to make rough estimates of reduced expenses for post-abortion care and lost income as a result of safer abortion with expanded access to mifepristone.

In the countries where mifepristone is registered or might be registered, the reduced hospitalization costs from averted abortions could be as high as US\$ 274 million in the scenario in which mifepristone costs US\$ 3.60. Lost income that could be regained by women could exceed US\$ 100 million. The averted hospitalization expenditure due to price reduction would be more than US\$ 70 million, and the regained income for women more than US\$ 27 million. In the context of total HRP expenditure (project and HRP staff costs combined), the last two figures represent benefit:cost ratios of 26:1 and 10:1, respectively, or 36:1 combined.

### **Economic analysis of use of mifepristone versus other methods of safe abortion**

The literature does not unambiguously show whether abortion provided medically is less expensive for the health system or for women than dilatation and curettage or manual vacuum aspiration. A study in Mexico showed that the total costs of medical abortion and manual vacuum

aspiration were approximately the same (Program for Appropriate Technology in Health, 2006a), while a study in Viet Nam indicated that medical abortion was significantly more expensive than manual vacuum aspiration (Program for Appropriate Technology in Health, 2006b). In the latter study, sensitivity analyses showed that overuse of ultrasound with medical abortion contributed to the higher cost and that lowering the cost of mifepristone could make medical abortion cheaper than manual vacuum aspiration or dilatation and curettage.

As mifepristone becomes better known among providers at all levels of service delivery, it is likely that the cost of medical abortion will decrease. Fewer follow-up visits will be needed, and they can be conducted by less expensive providers. Expensive equipment such as ultrasound would not be required in community facilities in developing countries, although investment in training providers to diagnose completeness of abortion would be necessary. In general, medical abortion is not a regimen that requires an elaborate service delivery setting.

The literature also does not indicate unambiguously whether more or fewer side-effects and more or less acceptability are associated with medical abortion in comparison with other safe methods of abortion. Creinin (2000) presented the results of a prospective study in the USA in which side-effects and patient acceptability of medical and surgical abortion were compared. He found fewer side-effects and better patient acceptability with surgical abortion. In an assessment of the literature, he found that studies in China, Cuba and India showed a greater incidence of side-effects, while both in his research and in research elsewhere, women who stated a strong preference for either method of abortion reported a positive experience with their chosen procedure.



# Future



## Lessons learnt

HRP has made a major impact on medical abortion by conducting clinically relevant, highly respected clinical trials, which have been the basis for national and international guidelines and which are applicable for service provision in developing countries. Given that the total expenditure on medical abortion in the past eight years was less than US\$ 1.7 million, the number, rigour and quality of the clinical trials produced is impressive.

HRP's work in the field has shown that producing clinical evidence and contributing to guidelines is not in itself sufficient for the technique to be adopted worldwide. Thus, HRP has worked with governments to help them define how medical abortion might most appropriately be introduced into their health services.

Lastly, and probably most importantly, HRP has worked with the Concept Foundation to produce a low-cost, prepackaged formulation that conforms to good clinical practice guidelines. The formulation has appropriate liability insurance (thus removing the need for local service providers to indemnify themselves against defective products) and can be made available through public services at an affordable price.

## Recommendations

### *Expenditure*

HRP's output in this area has been impressive, given the funds it has expended. As the budget available to HRP for medical abortion studies was greater than that spent, one could argue that HRP's inability to spend all the available resources limited its impact. If it is assumed that the budget was set to correspond to both the need for expenditure and planned activities, the lack of expenditure implies

that planned activities were not carried out. For example, the 2004 *Annual Technical Report* (WHO 2004) states that HRP wished to conduct a study to document the cost and cost-effectiveness of different methods of abortion by type of provider, but was unable to do so because of funding constraints. This may also be due to personnel limitations; in Gynuity Health Projects, 17 people are working in medical abortion, whereas in HRP only one person spends more than 50% of her time on this issue. HRP might wish to review how many of its planned activities in medical abortion are achieved and the reasons for the lack of spending on medical abortion. It should take steps to ensure that its spending is commensurate with the available budget in future years, including investing in more staff members, if necessary.

## Responsiveness of the WHO hierarchy

Medical abortion, and abortion provision in general, is one of the most controversial areas of the work of WHO. The aim is to prevent unsafe abortion, and WHO is not mandated to 'encourage' legislation of, and access to, abortion per se. Although HRP can publish scientific reports, it cannot be seen to be advocating abortion. The political sensitivity of this subject means that WHO publications on this issue are carefully reviewed by the Office of the Director-General and on occasion by the Office of Legal Counsel. This has caused delays in publication. WHO's Director-General's Office might wish to consider drawing up internal guidelines with HRP on how this issue is to be managed, with a target turn-around time of perhaps 30 working days between preparation of a report by HRP and approval for publication.

## Increasing the benefits

Several commentators have remarked that HRP might devote more resources to synthesis of evidence and systematic reviews. The guidelines produced by HRP, although based on the literature, have not gone through the arduous but rigorous procedures for generating evidence-based guidelines used, for instance, by the Cochrane Collaboration and the National Institute for Clinical Excellence (NICE) in the United Kingdom. Before HRP conducts further clinical trials, it would be appropriate to invest in such activities. The results would not only be publishable themselves (and thus inform clinicians) but would indicate the remaining uncertainties and the size and scope of studies required to address those uncertainties. The result would be that HRP could be more explicit about strategies that work (e.g. vaginal misoprostol) and thus provide appropriate evidence to countries considering introduction of less effective regimens.

## Future research

Although work on improving medical abortion regimens would add further to the literature base, the added value is likely to be less and less. HRP might wish to consider that fact before conducting further clinical trials (other perhaps than those required for registration of Medabon®) and instead focus on information required to improve access to medical abortion services. This might mean devoting more funds to research into barriers to service provision and access (public health and social science research) and less to clinical trials. This is in no way a criticism of the clinical trials that HRP has conducted to date: it is a testament to their importance and efficacy, indicating that HRP has addressed most of the clinically important questions in the design of medical abortion regimens.



# References



- Abuabara K, Blum S, eds. (2004). *Providing medical abortion in developing countries; an introductory guidebook*. New York, Gynuity Health Projects.
- Ahman E, Shah I (2004). *Unsafe abortion; global and regional estimates of the incidence of unsafe abortion and associated mortality in 2000*. Geneva, World Health Organization.
- Center for Reproductive Rights (2007). *Fact sheet: the world's abortion laws*. New York, NY.
- Creinin MD (2000). Randomized comparison of efficacy, acceptability and cost of medical versus surgical abortion. *Contraception*, 62:117–124.
- Elul B et al. (1999). Side effects of mifepristone–misoprostol abortion versus surgical abortion. Data from a trial in China, Cuba, and India. *Contraception*, 59:107–114.
- Grimes DA et al. (2006). Unsafe abortion: the preventable pandemic. *The Lancet*, 368:1908–1919.
- Harper CC et al. (2007). Reducing maternal mortality due to elective abortion: potential impact of misoprostol in low-resource settings. *International Journal of Gynaecology Obstetrics*, 98:66–69.
- Honkanen H et al. (2004). WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. *BJOG*, 111:715–725.
- Hord C et al. (1991). Reproductive health in Romania: reversing the Ceausescu legacy. *Studies in Family Planning*, 22:231–240.
- Khan KS et al. (2006). WHO analysis of causes of maternal death: a systematic review. *The Lancet*, 367:1066–1074.
- Kulier R et al. (2004). Medical methods for first trimester abortion. *Cochrane Database Systematic Reviews*, 2:CD002855.
- Ngoc NT et al. (2004). Is home-based administration of prostaglandin safe and feasible for medical abortion? Results from a multisite study in Vietnam. *BJOG*, 111:814–819.
- Program for Appropriate Technology in Health (2006a). *Costs of unsafe abortion in Mexico City*. Final report. Seattle, WA.
- Program for Appropriate Technology in Health (2006b). *Examining the cost of providing medical abortion in Vietnam*. Research report. Seattle, WA.
- Say L et al. (2002). Medical versus surgical methods for first trimester termination of pregnancy. *Cochrane Database Systematic Reviews*, 4:CD003037.
- Say L et al. (2005). Medical versus surgical methods for first trimester termination of pregnancy. *Cochrane Database Systematic Reviews*, 1:CD003037.
- Sedgh G et al. (2007a). Legal abortion worldwide: incidence and recent trends. *International Family Planning Perspectives*, 33:106–116.
- Sedgh G et al. (2007b). Induced abortion: estimated rates and trends worldwide. *The Lancet*, 370:1338–1345.
- Shah IH, Say L (2007). Maternal mortality and maternity care from 1990 to 2005: uneven but important gains. *Reproductive Health Matters*, 15:17–27.
- Tang OS et al. (1999). A randomized double-blind placebo-controlled study to assess the effect of oral contraceptive pills on the outcome of medical abortion with mifepristone and misoprostol. *Human Reproduction*, 14:722–725.
- Tang OS et al. (2002). The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial. *Human Reproduction*, 17:99–102.
- Vlassoff M (2006). *Economic impact of abortion related morbidity and mortality: modelling worldwide estimates*. Eldis Health Resource Guide (available at < <http://www.eldis.org/go/topics/resource-guides/health&id=32275&type=Document>>).

- von Hertzen H et al. (2006). WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. *BJOG*, 110:808–818.
- von Hertzen H et al. (2007). Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomized controlled equivalence trial. *The Lancet*, 369:1938–1946.
- Warriner I, Shah IH (2006). *Preventing unsafe abortion and its consequences*. New York, NY, Guttmacher Institute.
- WHO (1992). *The prevention and management of unsafe abortion. Report of a Technical Working Group*. Geneva, World Health Organization.
- WHO (2003). *Safe abortion: technical and policy guidance for health systems*. Geneva, World Health Organization.
- WHO (2004). *Annual Technical Report 2004*. Geneva, World Health Organization.
- WHO (2007). *Unsafe abortion, global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003*. 5th ed. Geneva, World Health Organization.
- World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2000). Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial. *BJOG*, 107:524–530.
- World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2001a). Lowering the doses of mifepristone and gemeprost for early abortion: a randomized controlled trial. *BJOG*, 108:738–742.
- World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2001b). Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial. *Acta Obstetrica et Gynecologica Scandinavica*, 80:447–451.



## Annex 1. Full text of paragraph 8.25 of the Programme of Action of the International Conference on Population and Development (Cairo, 1994)

The full text of paragraph 8.25, dealing with abortion, reads as follows:

In no case should abortion be promoted as a method of family planning. All Governments and relevant intergovernmental and non-governmental organizations are urged to strengthen their commitment to women's health, to deal with the health impact of unsafe abortion (defined in a footnote) as a major public health concern and to reduce the recourse to abortion through expanded and improved family planning services. Prevention of unwanted pregnancies must always be given the highest priority and all attempts should be made to eliminate the need for abortion. Women who have unwanted pregnancies should have ready access to reliable information and compassionate counselling. Any measures or changes related to abortion within the health system can only be determined at the national or local level according to the national legislative process. In circumstances in which abortion is not against the law, such abortion should be safe. In all cases, women should have access to quality services for the management of complications arising from abortion. Post-abortion counselling, education and family planning services should be offered promptly, which will also help to avoid repeat abortions.





## Annex 2. Clinical trials on medical abortion

World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2000) Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial. *British Journal of Obstetrics and Gynaecology*, 107:524–530.



The purpose of this study was to compare the efficacy of 200 mg mifepristone with 600 mg, both followed 48 h later by 0.4 mg of oral misoprostol to women whose menstruation was delayed by  $\leq 35$  days ( $\leq 63$  days' gestation). The rationale was to determine whether the cost of mifepristone could be reduced by using doses lower than 600 mg. This was a double-blind randomized study involving 1589 women in 17 centres, in Beijing, Havana, Helsinki, Ho Chi Min City, Hong Kong, Ljubljana, Melbourne, Moscow, Mumbai, Shanghai, Stockholm, St Petersburg, Szeged, Tbilisi, Tianjin, Tunis and Yerevan. The study showed that the two regimens had similar efficacy: 89.3% and 88.1% complete abortion rates with the lower and higher doses of mifepristone, respectively, 15 days after administration. There was a significant effect of increasing gestational age on the failure rate. The study was stopped early for women with 28–35 days' delayed menstruation, because the upper 95% confidence limit of the complete abortion rate had fallen below 90% (pre-specified stopping rule).

The importance of this study is that it provides evidence that 200 mg mifepristone is as effective as 600 mg, with the major cost benefit that this reduction brings. It also showed that 400  $\mu$ g misoprostol administered orally 48 h after 200 mg or 600 mg mifepristone was insufficiently effective to induce abortion in women with  $\geq 22$  days' menstrual delay. This finding was surprising, given that the registered regimen for mifepristone–misoprostol in Europe at the time was 600 mg mifepristone followed by 0.4 mg misoprostol.

The quality of the trial appeared high. Only 17 of the 1589 women were found not to have fulfilled the inclusion criteria appropriately, and only 35 women were lost to follow-up. The paper has been widely cited (43 citations as of November 2007).

World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation (2001a) Lowering the doses of mifepristone and gemeprost for early abortion: a randomized controlled trial. *British Journal of Obstetrics and Gynaecology*, 108:738–742.

The aim of this study was to test the efficacy of a lower dose of mifepristone and of gemeprost for medical abortion in women at  $\leq 56$  days' gestation. The rationale was to reduce both the cost and the incidence of side-effects associated with the high doses. Although previous studies had shown that 200 mg mifepristone was as effective as 600 mg in combination with an appropriate dose of prostaglandin, it was hoped that a further reduction in mifepristone dose might be possible.

A total of 1224 pregnant women were recruited to this double-blind randomized controlled trial in 13 cities: Aberdeen, Chandigarh, Edinburgh, Havana, Hong Kong, Ljubljana, Lusaka, Shanghai, Singapore, Stockholm, Szeged, Tbilisi and Tianjin. Women were randomized to one of four regimens consisting of mifepristone at 50 mg or 200 mg orally followed 48 h later by 0.5 mg or 1 mg gemeprost.



The incidence of complete abortion by the time of the next menstrual period was 87.3% in the group receiving 50 mg mifepristone and 92.1% in that receiving 200 mg (relative risk for failure, 1.6; 95% confidence interval, 1.1–2.3). Although the risk for failure was slightly greater in the group receiving the lower dose of gemeprost (relative risk, 1.3; 95% confidence interval, 0.9–1.8), this did not reach statistical significance.

The importance of this study is that it shows that lowering the dose of mifepristone from 200 mg to 50 mg is associated with a higher failure rate and is therefore unlikely to be helpful in practice. The study quality is high; there were only 18 protocol violations, and the outcome was unknown for only 16 women. The paper has been cited five times since publication, which is low.

von Hertzen H et al. (2003) WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. *British Journal of Obstetrics and Gynaecology*, 110:808–818.

The purpose of this study was to compare three misoprostol regimens, each given 48 h after 200 mg mifepristone to women at  $\leq 63$  days' gestation. The regimens were: 0.8 mg orally, followed by 0.4 mg orally twice daily for 7 days; 0.8 mg vaginally, followed by 0.4 mg orally twice daily for 7 days; and 0.8 mg vaginally with no additional misoprostol. The rationale was to determine whether a higher dose of misoprostol than that usually used (0.4 mg) would, in combination with mifepristone, be as effective as the mifepristone–gemeprost regimen. Misoprostol has advantages over gemeprost, in terms of both cost and stability at room temperature, but previous studies had shown that mifepristone followed by 0.4 mg misoprostol was insufficiently effective in women at more than 49 days' gestation.

A total of 2219 pregnant women were recruited in Beijing, Chandigarh, Helsinki, Ho Chi Minh City, Hong Kong, Ljubljana, Mumbai, New Delhi, Oslo, Shanghai, Singapore, Stockholm, Szeged, Targu Mures and Ulaanbaatar into this double-blind randomized controlled trial.

The complete abortion rates (assessed 6 weeks after treatment) were similar for women with amenorrhoea  $< 57$  days with the three misoprostol regimens (average, 93.1%). For women with  $\geq 57$  days' amenorrhoea, however, the complete abortion rate was 90.2% for those given the oral misoprostol regimen, 96.5% for the regimen with vaginal followed by oral administration, and 92.2% for the regimen with single vaginal misoprostol.

The importance of this study is that it shows that in women with  $\geq 57$  days amenorrhoea, misoprostol is more effective when administered vaginally rather than orally. Additionally, continuation of oral misoprostol further improves the complete abortion rate over that with a single vaginal dose of 0.8 mg misoprostol.

The quality of the trial was high. Only 29 women were lost to follow-up. The paper has been widely cited (23 citations as of November 2007).

Honkanen H et al. (2004) WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. *British Journal of Obstetrics and Gynaecology*, 111:715–725.



This paper reports further data from the previous study: those of side-effects and acceptability of the regimens. The study shows that, in addition to misoprostol being less effective when given orally (as described in the companion paper), side-effects of nausea, vomiting and diarrhoea were greater. Additionally, 84% of women would choose medical abortion again (compared to those who would prefer surgical abortion or who had no preference) and that 70% would choose to have future medical abortion, if needed, at health facility, compared to 23% of women preferring to be at home.

The importance of this paper is detailing the side-effects of possible regimens, which can be used in counseling women about their abortion options. Additionally, it suggests that a proportion of women may prefer medical abortion to be carried out at home.

The study quality is high, and the paper has been cited 14 times since publication (as of November 2007).

von Hertzen H et al. (2007) Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomized controlled equivalence trial. *The Lancet*, 369:1938–1946.

The purpose of this study was to compare four misoprostol regimens, two sublingual and two vaginal, and two given at a 3-h interval and two given at a 12-h interval. The rationale was to find an optimal medical abortion regimen with misoprostol alone for the many countries in which mifepristone is unavailable or too expensive. It was thought that the sublingual route might be a more effective alternative than the oral route, also obviating the need for vaginal administration, which might not be acceptable in some settings. Further, it was anticipated that shorter intervals between doses might hasten abortion and thus improve efficacy.

The study was a double-blind randomized controlled trial in 2066 women at  $\leq 63$  days' gestation recruited from centres in Hanoi, Havana, Ho Chi Minh City, Mumbai, New Delhi, Tbilisi, Trivandrum, Ulaanbataar and Yerevan. The treatment options were three doses of 0.8 mg misoprostol, given either vaginally at 3-h intervals, sublingually at 3-h intervals, vaginally at 12-h intervals or sublingually at 12-h intervals.

The study showed complete abortion rates (assessed two weeks after treatment) of 85% for vaginal administration at 3-h intervals, 84% for sublingual treatment at 3-h intervals, 83% for vaginal treatment at 12-h intervals and 78% for sublingual administration at 12-h intervals. The overall continuing pregnancy rate was 6%. Side-effects were most prevalent in the group given misoprostol sublingually at 3-h intervals.

The importance of this study is that it provides information on appropriate regimens for medical abortion with misoprostol alone, when mifepristone is unavailable. For women who do not wish to undergo vaginal administration, the sublingual route is an appropriate option, but the treatment interval must be



3 h rather than 12 h. These women should be counselled about the side-effects associated with this regimen.

This study is of high quality. Given that it was published only recently, it is too early to report the number of citations. Its importance can be inferred indirectly from the fact that it was published in *The Lancet*, a general medical journal with one of the highest impact factors, rather than a specialist obstetrics and gynaecology journal. Additionally, the paper was accompanied by a commentary, praising the study (which it described as 'technically complex' and 'a major logistical undertaking') and highlighting the importance of the misoprostol-alone strategy for abortion for many women around the world.

von Hertzen H et al. submitted.

The purpose of this study was to compare 100 mg with 200 mg mifepristone given 24 h or 48 h before 0.8 mg misoprostol administered vaginally. The rationale was to determine whether the dose of mifepristone can be reduced below 200 mg, thus reducing the cost, and to determine whether the interval between mifepristone and misoprostol administration could be reduced to 24 h, which is likely to be more acceptable to women and straightforward to organize in terms of health-care delivery.

A total of 2181 women at up to 63 days' gestation were randomized into four treatment groups: 100 mg mifepristone followed by 0.8 mg misoprostol 24 h later, 100 mg mifepristone followed by 0.8 mg misoprostol 48 h later, 200 mg mifepristone followed by 0.8 mg misoprostol 24 h later and 200 mg mifepristone followed by 0.8 mg misoprostol 48 h later. The study was designed as an equivalence study with a 5% margin of equivalence.

Fifty-five out of the 2181 women recruited were lost to follow-up. The four treatments were equally effective in the remaining women. Thus, 100 mg mifepristone followed 24 h later by 0.8 mg misoprostol is an appropriate treatment schedule to induce abortion in early pregnancy.

The importance of this study is that it allows a further reduction in the mifepristone dose. As the cost of mifepristone is a major component of the cost of medical abortion, this reduction in dose should reduce cost and therefore increase access. Additionally, it allows the process to be shortened, given that it shows that an interval of 24 h between mifepristone and misoprostol is as effective as the currently recommended interval of 48 h.

The report of this study has been submitted to *The Lancet*.

Two clinical trials were conducted by other researchers in the field during the period of review.

Ngoc NT et al. (2004) Is home-based administration of prostaglandin safe and feasible for medical abortion? Results from a multisite study in Vietnam. *British Journal of Obstetrics and Gynaecology*, 111:814–819.

This was a trial of patient preferences in Viet Nam, in which 1601 women underwent medical abortion with mifepristone at 200 mg followed 48 h later by 0.4 mg misoprostol given orally. Women were

offered the option of home or hospital treatment with misoprostol, and more than 80% selected the home option. Misoprostol administration at home did not reduce the efficacy of the treatment, and the majority of the women were satisfied with their treatment.

This study shows that home treatment with prostaglandin is likely to be safe, effective and acceptable. It might increase access to medical abortion, particularly for women who find hospital admission difficult or unpleasant. The quality of the study is good, less than 2% of women being lost to follow-up. The study was, however, confined to Viet Nam, thus limiting its generalizability to other developing countries.

Elul B et al. (1999) Side effects of mifepristone–misoprostol abortion versus surgical abortion. Data from a trial in China, Cuba, and India. *Contraception*, 59:107–114.

This trial addressed the side-effects associated with medical and surgical abortion in a comparative (largely nonrandomized) study of 1373 women in China, Cuba and India. This study gives useful information to help women choose between surgical and medical abortion.



## Annex 3. Strategic reviews



### Viet Nam

In response to the call by the 1994 International Conference on Population and Development (Cairo) to governments to reduce unsafe abortion, in 1995 the Ministry of Health of Viet Nam, in collaboration with WHO, decided to undertake a strategic assessment of abortion services to understand how to reduce the recourse to abortion and how to improve the safety and quality of the services being provided. The results were published as *UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. Abortion in Viet Nam: an assessment of policy, programme and research issues, 1999* (available at [http://www.who.int/reproductive-health/publications/HRP\\_ITT\\_99\\_2/abortion\\_in\\_viet\\_nam\\_assessment.pdf](http://www.who.int/reproductive-health/publications/HRP_ITT_99_2/abortion_in_viet_nam_assessment.pdf)). The report indicates that the Vietnamese Ministry of Health had, at that time, a growing interest in the use of mifepristone and misoprostol for medical abortion, as this strategy was seen to expand the options for women, increase privacy and potentially reduce the incidence of post-abortion infection and infertility associated with surgical abortion. The team concluded, however, that the proportion of women who might benefit from medical abortion in Viet Nam was low, because only national and provincial hospitals would be able to provide a service of appropriate quality and safety. Additionally, it was considered that the high cost of mifepristone would exclude poor women from accessing this option, and the high cost of mifepristone prevented the Ministry from providing medical abortion at prices similar to that of vacuum aspiration. The team concluded that scarce resources would better be invested in improving the quality of care of surgical services. The assessment did recommend that further research was necessary on a number of issues, including the provision of misoprostol at home after an initial

clinic visit, and this research was subsequently undertaken by the Population Council. Introduction of medical abortion was also added to research for improving the quality of comprehensive abortion care, implemented by the Ministry with support from Ipas. Mifepristone was subsequently registered in Viet Nam, and the method was included in national norms and guidelines. Although the price of mifepristone–misoprostol has been reduced substantially and the method is popular, it continues to be too expensive for most women.

### Romania

A similar strategic assessment was carried out in Romania. This country was a signatory to the International Conference on Population and Development (Cairo, 1994). The Romanian Ministry of Health and Family initiated the assessment and asked WHO for assistance. The assessment was based on the conceptual framework and strategic planning method drawn up by HRP. The focus of the review was to determine how to reduce the need for abortion, how to improve access to and the availability of post-abortion care and contraception, and how to improve the quality of abortion care and contraceptive services. The assessment was carried out in November 2001 and published in 2004 ([http://www.who.int/reproductive-health/publications/abortion\\_contraception\\_romania/text.pdf](http://www.who.int/reproductive-health/publications/abortion_contraception_romania/text.pdf)). Although medical abortion was not the focus of the review, it is one possible answer to Romania's need to reduce unsafe abortion, especially in rural areas. The main recommendation of the assessment team was to improve abortion and contraceptive services by a range of measures in comprehensive abortion care provision, including the introduction of medical abortion if and where feasible. It noted that medical abortion had been introduced in Romania in 1999 through a WHO clinical trial and had proven popular

with women. The issue of cost, both of abortion and contraceptive services, was again highlighted as a barrier to access.

## Mongolia

A similar strategic assessment was undertaken in Mongolia (2005 technical report). Mifepristone and misoprostol have been registered in Mongolia, and providers were trained in their use (with help from HRP) for both first- and second-trimester abortion. Medical abortion protocols are now included in the national norms and standards in Mongolia, approved in September 2005.

## Moldova and Ghana

Following strategic assessments focusing on preventing unintended pregnancies and the quality of abortion and post-abortion services, in collaboration with HRP, in Moldova and Ghana, a series of recommendations (including introduction of medical abortion) were generated, and activities are under way. Medical abortion protocols are included in the national norms and standards for comprehensive abortion care in Ghana, approved in 2006.



## Annex 4. Selected publications from HRP during the review period



### 2007

von Hertzen H et al. (2007). Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomized controlled equivalence trial. *The Lancet*, 369:1938–1946.

WHO (2007). Unsafe abortion. *Global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003. Fifth edition*. Geneva, World Health Organization.

### 2006

Åhman E, Shah I (2006). Contraceptive use, fertility and unsafe abortion in developing countries. *European Journal of Contraception and Reproductive Health Care*, 11:126–131.

### 2005

Chan CCW et al. (2005). Intracervical sodium nitroprusside versus vaginal misoprostol in first trimester surgical termination of pregnancy: a randomized double-blinded controlled trial. *Human Reproduction*, 20:829–833.

Ministry of Health, Ghana (2005). *Abortion and abortion care services in Ghana: a strategic assessment of policy, programme and research issues*. Accra, Ministry of Health.

Ministry of Health, Republic of Moldova (2005). *Abortion and contraception in the Republic of Moldova: a strategic assessment of policy, quality and access issues related to fertility regulation services*. Chisinau, Ministry of Health.

Mittal S et al. (2005). Comparison of oral versus vaginal misoprostol and continued use of misoprostol after mifepristone for early medical abortion. *Indian Journal of Medical Research*, 122:132–136.

Nguyen Duc Vy, Nguyen Thi My Huong (2005). Comparison of the safety and the quality of manual vacuum aspiration (MVA) performed by physicians and mid-level health providers in Viet Nam. *Journal of Obstetrics and Gynaecology-VINAGOFPA*, special issue:313–319.

Nguyen Duc Vy, Nguyen Thi My Huong (2005). Comparison of the safety and the quality of manual vacuum aspiration (MVA) performed by physicians and mid-level health providers in Viet Nam. *Journal of Military Pharmaco-Medicine*, 30:16–22.

Shah R, Baji S, Kalgutkar S (2005). Attitudes about medical abortion among Indian women. *International Journal of Gynaecology and Obstetrics*, 89:69–70.

Tang OS et al. (2005). A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Human Reproduction*, 20:3062–3066.

### 2004

Åhman E, Shah I (2004). *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2000, fourth edition*. Geneva, World Health Organization.

Aronsson A, Bygdeman M, Gemzell-Danielsson K (2004). Effect of misoprostol on uterine contractility following different routes of administration. *Human Reproduction*, 19:81–84.

Hoffman M et al. (2004). Comparison of the safety and satisfaction of first-trimester abortions in South Africa: Methods. Poster presented at 11th Reproductive Health Research Priorities, Sun City, South Africa.

Honkanen H et al. (2004). WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion: II Side effects and women's perceptions. *BJOG*, 111:715–725.

Johnson BA, Horga M, Fajans P (2004). A strategic assessment of abortion and contraception. *Reproductive Health Matters*, 12:184–194.



Kulier R et al. (2004). Medical methods for first trimester abortion. *Cochrane Database of Systematic Review, Issue 1. Art. No.: CD002855s.*

Marston C, Cleland C (2004). *The effects of contraception on obstetric outcomes.* Geneva, World Health Organization.

Ministry of Health and Family, Romania (2004). *Abortion and contraception in Romania: a programme and research issues.* Bucharest, Ministry of Health and Family, Romania (English version submitted).

Shah I, Åhman E (2004). Age patterns of unsafe abortion in the developing country regions. *Reproductive Health Matters*, 12:9–17.

Tang OS et al. (2004). A prospective randomized comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG*, 111:1001–1005.

## 2003

Bygdeman M (2003). The possibility to use mifepristone for menstrual induction. *Contraception*, 68:495–498.

Chan CCW et al. (2003). The effect of mifepristone on the expression of steroid hormone receptors in human decidua and placenta: a randomized placebo-controlled double-blind study. *Journal of Clinical Endocrinology and Metabolism*, 88:5846–5850.

Heikinheimo O et al. (2003). Pharmacokinetics of mifepristone in the human reveal insights into differential mechanisms of antiprogesterin action. *Contraception*, 68:421–426.

Heikinheimo O et al. (2003). Termination of pregnancy with mifepristone and prostaglandin suppresses transiently circulating glucocorticoid bioactivity. *Journal of Clinical Endocrinology and Metabolism*, 88:323–326.

Hewage P (2003). Illegal cases of induced abortion reported to professional providers of health services in Colombo district of Sri Lanka. Paper presented at 2nd Asia Pacific Conference on Reproductive and Sexual Health, Bangkok, Thailand, 6–10 October 2003.

Hewage P (2003). Profile of abortion seekers in the Colombo district and reasons for having induced abortion. Programme of abstracts of the first academic sessions. University of Ruhuna, Matara, Sri Lanka.

Hewage P (2003). Unwanted pregnancy and induced abortion: experience of married women in Colombo district. Programme and abstracts. Sixth Annual Session, Population Association of Sri Lanka.

Marston C, Cleland J (2003). Relationships between contraception and abortion: a review of the evidence. *International Family Planning Perspectives*, 29:6–13.

Mongolian Public Health Institute (2003). *A strategic assessment of policy, program and research issues related to reducing the recourse to abortion and improving the quality of care of abortion and family planning services in Mongolia.* Ulaanbaatar, Mongolian Public Health Institute.

Piaggio G, von Hertzen H, Elbourne D (2003). Ethical aspects and stopping rules in equivalence trials: two case studies [abstract]. *Controlled Clinical Trials*, 24:90S.

Sitruk-Ware R, Spitz IM (2003). Pharmacological properties of mifepristone toxicology and safety in animal and human studies. *Contraception*, 68:409–420.

Tang OS et al. (2003). A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. *Human Reproduction*, 18:2315–2318.

von Hertzen H et al. (2003). WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion: I. Efficacy. *BJOG*, 110:808–818.

Xiao B et al. (2003). Menstrual induction with mifepristone and misoprostol. *Contraception*, 68:489–494.





Xiao B et al. (2003). Luteal phase treatment with mifepristone and misoprostol for fertility regulation. *Contraception*, 68:477–482.

## 2002

Åhman E, Shah I (2002). Unsafe abortion: worldwide estimates for 2000. *Reproductive Health Matters*, 10:13–17.

Åhman E, Dolea C, Shah I (2002). Global burden of abortion in the year 2000. In: *Global Burden of Disease 2000*. Geneva, World Health Organization.

Ganatra B, Hirve S (2002). Induced abortion among adolescent women in rural Maharashtra, India. *Reproductive Health Matters*, 10:76–85.

Gogna M, Petracci M, Romero M, Ramos S, Szulik D (2002). Abortion in a restrictive legal context: the views of obstetrician–gynaecologists in Buenos Aires, Argentina. *Reproductive Health Matters*, 10:128–137.

Hewage P (2002). Cases of induced abortion reported to the health professionals in Colombo district. *Journal of the Faculty of Humanities & Social Sciences, Vol. 3*. Colombo, University of Ruhuna, Matara, Sri Lanka, 10–18.

Honkanen H, von Hertzen H (2002). Acceptability of medical abortion in Finland. *Contraception*, 65:419–423.

Tang OS, Lee SWH, Ho PC (2002). A prospective randomized study on the measured blood loss in medical termination of early pregnancy by three different misoprostol regimens after pretreatment with mifepristone. *Human Reproduction*, 17:2865–2868.

Tang OS, Lee SWH, Ho PC (2002). The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial. *Human Reproduction*, 17:99–102.

Tang OS, Schweer H, Seyberta HW, Lee SW, Ho PC (2002). Pharmacokinetics of different routes of administration of misoprostol. *Human Reproduction*, 17:332–336.

Van Look PFA, Cottingham JC (2002). Unsafe abortion: an avoidable tragedy. *Best Practice and Research. Clinical Obstetrics and Gynaecology* 16:205–220.

von Hertzen H et al. for the WHO Research Group on Post-ovulatory Methods of Fertility Regulation (2002). Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *The Lancet*, 360(9348):1803–1810.

## 2001

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Post-ovulatory Methods of Fertility Regulation (2001). Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost: a randomized controlled trial. *Acta Obstetrica et Gynecologica Scandinavica*, 80:447–451.

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Post-ovulatory Methods of Fertility Regulation (2001). Lowering the doses of mifepristone and gemeprost for early abortion: a randomized controlled trial. *BJOG*, 108:738–742.

## 2000

Indian Council of Medical Research Task Force (2000). A multicentre randomised comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE2 gel (meteneprost) or 600 µg oral PGE1 (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. *Contraception*, 62:125–130.

## Annex 5. Percentage of medical abortions among all abortions in selected countries, 2006

Country/area	Total number of abortions in 2006	Number of medical abortions in 2006	Percentage
China	7–9 000 000	2–3 000 000	28–30
Denmark	15 000	4950	33
England and Wales	186 400	44 740	24
Finland	11 000	5830	53
France	161 130	70 000	44
India	6–7 000 000	2 760 000 (?)	40 (?)
Norway	13 670	5200	38
Russian Federation	1.6–2.7 000 000	NA	NA
Scotland	12 600	7410	58
South Africa	85 600	5000 (?)	6 (?)
Sweden	37 500	18 550	53
Turkey	400 000 (?)	0	0
Ukraine	3–400 000	NA	NA
USA	1 210 000	135 000	11
Viet Nam	800 000 (?)	50 000 (?)	6 (?)

NA = Not available

(?) = Uncertain figure

Source: Peter Hall, 2007, personal communication



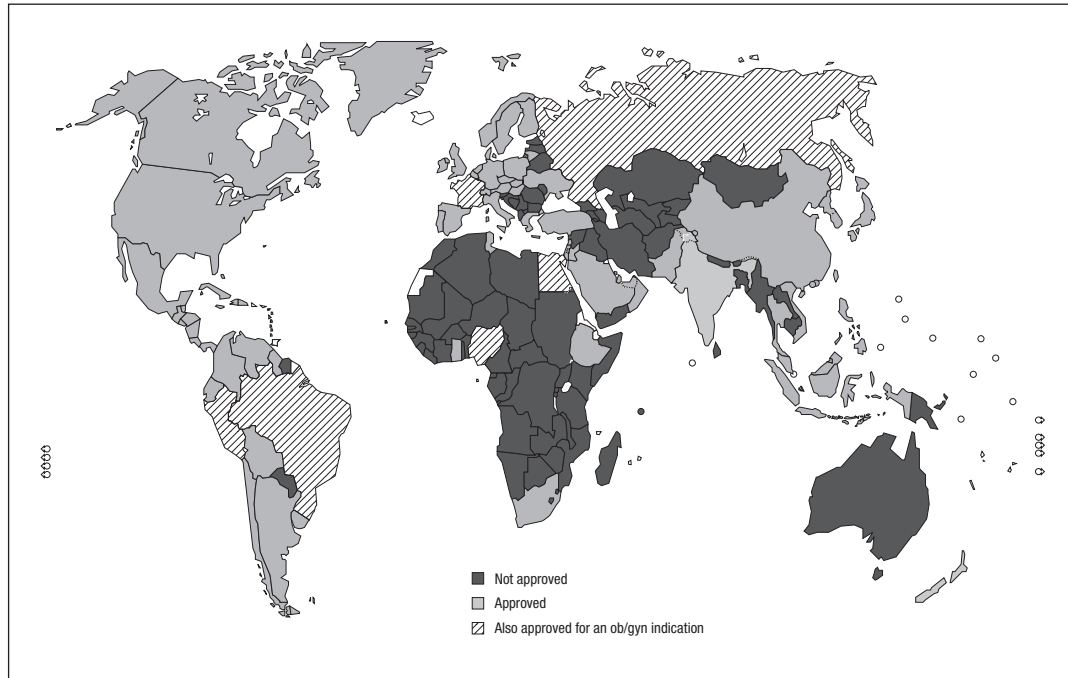
## Annex 6. Countries and year of approval of mifepristone



Year	Countries
1988	China, France
1991	United Kingdom
1992	Sweden
1999	Austria, Belgium, Cyprus, Denmark, Finland, Germany, Greece, Israel, Netherlands, Spain
2000	Norway, Russian Federation, Tunisia, United States of America
2001	New Zealand, South Africa
2002	Azerbaijan, Belarus, Georgia, Latvia, Serbia, Uzbekistan
2003	Estonia
2004	Guyana
2005	Hungary, Mongolia
2007	Portugal

Source: Gynuity Health Projects: <http://www.gynuity.org>


## Annex 7. Countries of approval of misoprostol



Source: Gynuity Health Projects: <http://www.gynuity.org>

## Annex 8. Economic costs of medical abortion

Table 1. Estimates of potential economic costs averted as a result of averted abortions



	Number of unsafe abortions averted	Post-abortion hospitalization costs potentially averted, millions of US\$	Saved income for women, millions of US\$
Scenario 1: Abortion free and fully accessible	9 052 215	634.99	243.6
Scenario 2: Abortion free and accessible to women with access to maternal health services	4 754 131	333.49	127.9
Scenario 3: Mifepristone available at US\$3.60 and accessible to women with access to maternal health services	3 907 006	274.07	105.1
Scenario 4: Mifepristone available at US\$15 and accessible to women with access to maternal health services	2 895 964	203.14	77.9
Abortions averted as a result of the price decrease	1 011 041	70.92	27.2

For each of these scenarios of improved access, the number of averted unsafe abortions and averted maternal mortality (Annex 3) were estimated using the following formulae:

$$\text{UnSafeAbortionsAverted}_{ij} = \text{NumWom15-44}_{ij} \times \text{IncAbortion}_i$$

UnSafeAbortionsAverted is the potential number of unsafe abortions averted.

NumWom15–44 is the number of women aged 15–44<sup>a</sup>.

IncAbortion is the regional incidence rate of abortion (annual abortions per 1000 women)<sup>b</sup>.

“i” is the indices of regions.

“j” is the indices for one of two markets: countries with a potentially conducive legal structure or countries with both a conducive legal structure and ability to pay.

$$\text{MortAverted}_{ij} = \text{UnSafeAbortionsAverted}_{ij} \times (\text{MortalityRatio}_j / \text{IncidenceRatio}_j)$$

MortAverted is the potential number of maternal deaths averted<sup>c</sup>.

MortalityRatio is the abortion deaths per 100 000 live births<sup>d</sup>.

IncidenceRatio is the number of abortions per 1000 live births<sup>e</sup>.

“i” is the indices of regions.

“j” is the indices for one of two markets: countries with a potentially conducive legal structure or countries with both a conducive legal structure and ability to pay.

<sup>a</sup> *World population prospects: the 2006 revision*. New York, United Nations Population Division, Department of Social and Economic Affairs, 2007.

<sup>b</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003*. Geneva, World Health Organization, 2007.

<sup>c</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003*. Geneva, World Health Organization, 2007.

<sup>d</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003*. Geneva, World Health Organization, 2007.

<sup>e</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003*. Geneva, World Health Organization, 2007.

Table 2. Percentages of population able to pay US\$ 15 and US\$ 3.60 according to gross national income per capita

Gross national income per capita (US\$)	Percentage of population able to pay at US\$ 15	Percentage of population able to pay at US\$ 3.60
0–500	10	50
501–1000	50	75
1001–2000	50	95
2001–5000	75	95
≥ 5001	95	95



## Annex 9. Annual estimates of potential unsafe abortions and maternal deaths averted in countries where mifepristone is registered or likely to be registered



	Latin America & Caribbean	Africa	South Central Asia	Asia	Europe	World
<b>Scenario 1: Medical abortion free and fully accessible</b>						
Unsafe abortions averted	421 806	2 477 599	4 967 471	733 030	452 309	9 052 215
Maternal deaths averted	250	16 255	18 628	828	60	36 024
<b>Scenario 2: Medical abortion free and accessible to women with access to maternal health services</b>						
Unsafe abortions averted	406 776	1 014 851	2 212 846	670 502	449 155	4 754 131
Maternal deaths averted	241	4 890	8 298	758	60	14 250
<b>Scenario 3: Mifepristone available at US\$ 3.60 and accessible to women with access to maternal health services</b>						
Unsafe abortions averted	386 437	814 431	1 660 218	619 222	426 698	3 907 006
Maternal deaths averted	229	3 460	6 226	703	60	10 677
<b>Scenario 4: Mifepristone available at US\$ 15 and accessible to women with access to maternal health services</b>						
Unsafe abortions averted	310 369	601 052	1 102 625	498 457	383 462	2 895 964
Maternal deaths averted	186	2 125	4 135	542	54	7 041
<b>Abortions and maternal deaths averted as a result of the price decrease</b>						
Unsafe abortions averted	76 069	213 379	557 593	120 765	43 236	1 011 041
Maternal deaths averted	44	1 336	2 091	161	6	3 637
<b>Abortions and maternal deaths in 2003</b>						
Total unsafe abortions 2003 <sup>a</sup>	3 900 000	5 500 000	6 300 000	3 500 000	500 000	19 700 000
Total deaths due to abortions 2003 <sup>b</sup>	2 000	36 000	24 300	4 100	<60	66 500

<sup>a</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003.* Geneva, World Health Organization. 2007.

<sup>b</sup> *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003.* Geneva, World Health Organization. 2007.