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Long-term safety and effectiveness of copper-releasing intrauterine devices: a case-study

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Executive summary

HRP's research programme on intrauterine devices (IUDs) was initiated in 1972. At that time, multiple models existed, but their safety and efficacy had not been established in appropriate clinical trials. HRP's research was designed to provide information on the safety of existing IUDs, the duration of effectiveness of copper IUDs, their mechanism of action and their relation to pelvic inflammatory disease. Another goal was to prepare internationally acceptable evidence-based guidelines for service delivery. These goals provided the foundation for HRP's extended IUD research initiative.

Methods

Four main methods were used to obtain the information included in this report: personal interviews and continuous communication with HRP staff in Geneva; interviews with 21 experts on IUD research and use, in various geographical regions and institutions; review of a large number of HRP documents and publications; and analysis of national data on IUD use to estimate the impact of HRP's work.

Findings

The major milestones in HRP's work on IUDs have been:

- establishment in 1972 of the Task Force on Intrauterine Devices for Fertility Regulation, which provided the necessary research infrastructure to the programme and improved research capability in developing countries to allow them to conduct research on other aspects of sexual and reproductive health of national or international interest,
- provision of data for approval in 1994 of the TCu 380A device by the United States Food and Drug Administration for 10 years of use; and

- publication of *Medical eligibility criteria for contraceptive use*, *Selected practice recommendations for contraceptive use*, the *Decision-making tool for family planning clients and providers* and *Family planning: a global handbook for providers*, which became the standard references guiding delivery of IUD services worldwide.

HRP's IUD research between 1972 and 2007 included 21 randomized and seven non-randomized clinical trials, 11 studies on menstrual blood loss, 10 on the mechanism of action of IUDs, seven on new IUDs, three on agents to treat excessive bleeding, three on special safety issues and one on the demographic and economic impacts of IUD use. These studies resulted in 156 publications, which form a major portion of the global body of scientific evidence on the safety and efficacy of IUDs.

The main outcomes of the programme have been: establishing the duration of contraceptive effectiveness and safety of copper IUDs; consensus-based, internationally accepted guidelines for the use of IUDs; evidence of a low risk for pelvic inflammatory disease associated with IUD use; and the mechanism of action of IUDs.

The main global public good has been establishment of the TCu 380A as a safe, highly effective long-term contraceptive, expanding the limited choices women have for such methods. It is estimated that, between initiation of the HRP programme and 2007, the number of IUD users increased from 70 million to 160 million, and it is reasonable to attribute an important part of this increment to the Programme. HRP research also established that the primary mechanism of action of the TCu 380A is prevention of fertilization and that the risk for pelvic inflammatory disease is low. Updated IUD guidelines have been incorporated into numerous country norms. Our analysis of the most





recent data indicates that increasing the duration of use and the number of IUD users can have a major impact on global health and economy.

HRP's research programme has been cost-effective. In 1990, 45 scientists in 15 countries conducted clinical trials on the TCU 380A, TCU 220C, Multiload 375, a new frameless IUD and an implantable post-placental IUD. The total research expenditure for that year was US\$ 78 000, a fraction of the cost of similar trials by other organizations. The cost of conducting high-quality clinical trials has increased substantially over the past few years, mainly due to the exigencies of good clinical practice, research ethics and national regulations. The favourable cost differential between HRP and other public sector research organizations will continue, but probably at a reduced level. We consider, however, that conducting research with HRP is more than a cost-saving alternative: HRP provides important advantages for changes in policies and practice, including its national and international recognition and its influential relations.

HRP's research on IUDs has built effectively on the work of other organizations. In addition, it has collaborated with numerous national and international training and service delivery organizations to increase the health impact of IUDs.

A finding that will require special attention is the persistent discrepancy between the scientific evidence from HRP and other organizations and the perspectives of providers and the public. Our interviews with IUD experts indicate that, in many countries, there is still a belief that the TCU 380A is effective for less than 10 years, that it prevents implantation or is an abortifacient, and that it causes a high rate of pelvic inflammatory disease. Programme and translational research must be

strengthened to overcome these barriers and misconceptions.

We identified differing perceptions of the role of HRP in translating research results into practice. Some considered that HRP is responsible only for research, publication and dissemination, while others considered that it should be responsible for the health and economic impacts of its research. This requires further clarification.

Conclusions

- The goals of the HRP research agenda, established in 1972, to provide relevant information to country programmes have been fully and successfully achieved. There is a general perception that the essential clinical research on copper IUDs is almost complete, with the possible exception of additional research on the relation between IUD use and HIV/AIDS.
- A disturbing gap persists between the available scientific evidence and the perceptions of providers and the public. This area requires continued effort.
- Development of the TCU 380A and its introduction into programmes is the result of the collective work of numerous national and international organizations.

Recommendations

- Strengthen the 'research into practice' strategy of HRP/RHR¹. Service and medical barriers persist that continue to limit the use of IUDs.

1. The Department of Reproductive Health and Research (RHR) includes HRP and a component concerned with programmatic work in sexual and reproductive health.

- Define the level of impact of IUDs for which HRP/RHR is responsible. Identify appropriate indicators for that impact.
- Strengthen the collaboration between HRP/RHR and WHO regional and country offices, other international organizations and national stakeholders to enhance the translation of research into practice.

Methods

The main sources of information for this report were interviews with HRP staff responsible for the IUD programme in Geneva; interviews with non-HRP staff with long experience in IUD research and services in different geographical areas; review of many HRP documents related to its IUD work; and analysis of available information on use of IUDs in countries.

On 19–21 September 2007, Roberto Rivera, the writer of this case-study, had long working sessions with the HRP staff responsible for IUD work. Before this visit, he was in regular e-mail or telephone communication with the responsible person at HRP, from whom he received relevant documents and with whom he had conversations that outlined the agenda and the persons he should meet in Geneva. Once in Geneva, he had long meetings with several staff members, who remained available at all times during his three-day stay. They provided extensive information, responded to all his questions and furnished the materials he requested. Communication continued after his visit, until this report was finished. He had the opportunity to speak with HRP staff who had been involved in IUD research since it was initiated in 1972.

Between 28 August and 27 September 2007, 21 persons were interviewed to obtain qualitative information relevant to this evaluation. The aim

was to understand the range of views held, and not their frequency or distribution. For this purpose, the convenience sample size of 21 can be considered adequate. These persons were associated with international agencies, HRP collaborating research centres, ministries of health or national family planning programmes. All had extensive knowledge of IUD research and use. In these interviews, a structured questionnaire was used which was based on the questionnaire used for the 1990–2002 external evaluation, adapted for this case-study. The characteristics of the interviews are presented in Table 1.

Table 1. Characteristics of interviews

Number of persons interviewed	21
Males	14
Females	7
Location	
Africa	3
Asia	4
Eastern Europe	1
Latin America	9
USA	4
Manner of interview	
Face-to-face interviews	4
Telephone interviews	7
E-mail interviews	10

We reviewed a large number of journal publications, documents and information produced by HRP staff on request. In particular, and due to the support of HRP staff, Roberto Rivera was able to review the IUD sections of all the HRP Annual Reports, from 1973 to 2006.

Available data on IUD use in various developing countries were analysed to assess the potential health and economic impact of increasing the duration of use or the number of IUD users.





Rationale

IUDs are the most commonly used reversible method of contraception worldwide. Several factors account for this level of use, namely its degree of safety and its high efficacy with no difficult requirements of the user for its correct and continued use. In the early 1970s, when HRP initiated its research on IUDs, there were estimated to be approximately 70 million IUD users worldwide. Multiple IUD models existed, several of them containing copper, but the safety and efficacy of these devices had not been established in appropriate clinical trials. The relative advantages and disadvantages of these IUDs were unknown. Pressing questions for programmes and providers were:

- What is the relative safety and effectiveness of the different IUDs?
- What is the safety and effectiveness of IUDs inserted at different times, e.g. postpartum, postabortion or after an interval?
- What is the duration of the contraceptive effectiveness of these devices?
- What is the mechanism of action of the contraceptive effect of IUDs?
- What are the risks for pelvic inflammatory disease or ectopic pregnancy associated with the use of IUDs?
- How important is, and what are the consequences of, the increased menstrual blood loss associated with the use of IUDs?
- What are the safety and efficacy of different treatments for controlling excessive menstrual bleeding associated with the use of IUDs?
- What clinical guidelines should be recommended for the safe provision of IUDs?

The HRP IUD research programme was initiated and designed to provide answers to these questions to governments and family planning programmes, particularly in developing countries. This research programme was clearly within HRP's mandate to promote, conduct, evaluate and coordinate international research on sexual and reproductive health. This goal-oriented research agenda ensured the consistency, continuity and effectiveness of the Programme.

Process

The milestones of the HRP IUD research programme are described below.

- In 1972, HRP initiated its IUD research programme and the Task Force on Intrauterine Devices for Fertility Regulation was created, involving 31 scientists from 13 countries. The first clinical trial was on a progesterone-releasing device.
- In 1975, the first comparative clinical trials of copper IUDs were initiated, including the three devices most commonly used at that time (outside China): the Lippes loop, Cu 7 and TCu 220C, inserted after therapeutic termination of pregnancy and after spontaneous abortion.
- In 1976, the first studies of menstrual blood loss after insertion of the Lippes loop, Cu 7 and TCu 220C were initiated.
- In 1978, on the basis of HRP experience, WHO advised against further use of the Lippes loop in family planning programmes. The same year, a case–control study of the association between IUD use and pelvic inflammatory disease and ectopic pregnancy was initiated.

- In 1980, a randomized clinical trial of the TCu 220C and TCu 380A was initiated.
- In 1981, WHO was informally involved in setting the first IUD standards.
- In 1982, the State Family Planning Commission of China identified research on IUDs as a priority, and HRP was asked to assist in setting up and monitoring the Chinese research strategy.
- In 1985, the Task Force on IUDs was subsumed into the newly created Task Force on Safety and Efficacy of Fertility Regulating Methods.
- In 1986, Member States asked for WHO advice on the safety and efficacy of IUDs, as companies were withdrawing products from the market. A scientific group met in December 1986.
- In 1989, a randomized clinical trial on the TCu 380A and Multiload 375 was initiated.
- In 1990, the TCu 380A was approved for eight years of use by the United States Food and Drug Administration on the basis of HRP data.
- In 1991, the Scientific and Technical Advisory Group endorsed establishment of IUD research as a separate budget line and a research group on IUDs, with a strategic plan formulated by a Steering Committee, was set up. The influential HRP study establishing the relationship between IUD use and pelvic inflammatory disease was published.
- In 1993, a randomized clinical trial of the TCu 380A and the levonorgestrel-releasing IUD Mirena was initiated.
- In 1994, the TCu 380A was approved for 10 years of use by the United States Food and Drug Administration on the basis of HRP data.
- In 1996, RHR published the first edition of the highly influential *Medical eligibility criteria for contraceptive use* (including IUDs) (WHO, 2004).
- In 1997, RHR published the first edition of *Selected practice recommendations for contraceptive use* (including IUDs) (WHO, 2005a). A study of use of TCu 380A for emergency contraception was initiated in China.
- In 1998, RHR published the *Decision-making tool for family planning clients and providers*.
- In 2004, data on the effectiveness of the TCu 380A after 12 and 13 years were made available to the United States manufacturer for submission to the United States Food and Drug Administration. It is our understanding that these data were submitted; however, we have no knowledge of any response from this agency confirming that the currently approved 10-year duration might be increased.
- In 2006, HRP coordinated a meeting of the IUD Technical Review Committee to advise the International Standards Organization (ISO) on IUD standards.
- In 2007, RHR, in collaboration with the Johns Hopkins Bloomberg School of Public Health and the United States Agency for International Development, published *Family planning: a global handbook for providers* (WHO, 2007). Evidence-based guidance was generated through worldwide collaboration.

This research agenda involved literally hundreds of research sites and investigators in dozens of countries. As a result, capability was created to conduct high-quality clinical trials, particularly in developing countries. Furthermore, the IUD research and the institutional strengthening component of HRP contributed to the establishment and functioning of numerous research institutions





worldwide, again particularly in developing countries. This HRP investment has benefited not only its IUD research programme but all research activities conducted by HRP, and it has increased the capability of countries to conduct other research of national interest or research sponsored by other organizations. The research system of HRP, through the IUD Steering Committee and Task Force, allowed for continuous interaction with investigators and research sites. Owing to limited resources, however, monitoring of the clinical trials conducted in many sites and countries was also limited. This sometimes resulted in problems with data management and verification, which delayed the completion of studies.

Outputs

HRP-supported IUD research between 1972 and 2007 resulted in 21 randomized controlled clinical trials, conducted in multiple centres and countries; seven non-randomized trials conducted in China, Mongolia and Viet Nam; and 11 studies of menstrual blood loss, conducted in Brazil, Chile, China, England, Japan, Mexico, the Republic of Korea, Sweden, the USA and Zambia. There were also three studies of agents to treat IUD-induced endometrial bleeding, 10 studies on the mechanism of action of IUDs, seven studies of new devices and three studies on special issues related to IUD safety. One study was an analysis of the economic and public health impact of IUD use in China. The studies addressed the progesterone-releasing IUD, Lippes loop, Cu 7, Saf-T-coil, TCu 200, TCu 220C, TCu 380A, Multiload 250, Multiload 375, Nova T, Flexigard, Shanghai V, Mahua ring, the Chinese stainless-steel ring and two other Chinese rings, chloroquine-releasing IUD, noresthisterone-releasing IUD, WHO levonorgestrel-releasing IUD and Mirena (see also Annex 1).

HRP-supported IUD research resulted in 156 formal publications in leading national and international journals, which collectively form a major portion of the global body of scientific evidence for the safety and efficacy of copper IUDs. These publications are listed in Annex 2.

In 1996, RHR published the first edition of the *Medical eligibility criteria for contraceptive use* (WHO, 2004) and the *Selected practice recommendations for contraceptive use* (WHO, 2005a), which became the basis for most of the guidelines currently used for the delivery of IUD services.

In 2007, on the basis of technical information in the two above-mentioned publications, RHR in collaboration with the Johns Hopkins Bloomberg School of Public Health and the United States Agency for International Development published *Family planning: a global handbook for providers* (WHO, 2007). This book translates scientific information into practical guidance for all major contraceptive methods.

Outcome

The interviews with non-HRP staff conducted for this evaluation included a question on what the interviewees considered to be the most important outcomes of HRP's work in the past 10 years, although some respondents answered the question without a 10-year limit. The first four areas listed below were clearly seen as most important outcomes of HRP's work.

- *Establishing the duration of the contraceptive effectiveness of the various copper IUDs.* The comparative cumulative pregnancy rates after 5, 7 and 9 years were 1.5, 1.7 and 2.1 per 100 woman-years, respectively, for the TCu 380A, and 4.0, 4.9 and 5.4, respectively,

for the TCU 220C. The pregnancy rate up to 10 years of use of the TCU 380A was 2.3. The results of this study were submitted to the United States Food and Drug Administration in 1993, which approved, in 1994, the TCU 380A for up to 10 years of use on the basis of this information. HRP-supported comparative trials of the TCU 380A and the Multiload 375 showed that the two were of comparable safety and effectiveness.

- *Establishing the safety and efficacy of copper IUDs.* This outcome was precisely one of the objectives of HRP when the IUD research programme was initiated in the early 1970s. One of the persons interviewed by telephone said: “HRP produced the basis of the scientific evidence on the safety and efficacy of IUDs, no other organization would have been able to do it.” As a result of the HRP studies, the TCU 380A is currently considered the reference IUD in terms of safety and effectiveness.
- *Preparation of the Medical eligibility criteria for contraceptive use and the Selected practice recommendations for contraceptive use.* These two documents have had a strong influence on the delivery of IUD services. All the interviewees who mentioned these two documents as among the most important outcomes of HRP were in developing countries.
- *Establishing the relation between IUD use and pelvic inflammatory disease and the mechanism of action of IUDs.* There is general recognition that the best information currently available on the level of risk for pelvic inflammatory disease associated with IUD use came from a study by HRP of 22 908 insertions and 616 790 woman–months of experience. The overall rate of pelvic inflammatory disease was 1.6 per 1000 woman–years of use, and the rate in the first 20 days after insertion was 9.7.
- *Establishing the amount of menstrual blood loss associated with use of various IUDs and its management.* It is known that there is a dissociation between a woman’s perception of menstrual blood loss and the actual loss. In carefully executed worldwide studies, HRP established the actual amount of menstrual blood loss with different IUDs, less blood being lost with the copper IUDs, particularly the TCU 220C and the TCU 380A, than with non-copper containing IUDs. In subsequent HRP-supported studies, the effectiveness of various non-steroidal anti-inflammatory drugs in reducing excessive menstrual blood loss was demonstrated.
- *Producing the best information currently available on the mechanism of the contraceptive action of copper IUDs.* HRP-cosponsored studies conducted in the HRP collaborating research centre in Santiago, Chile, and in Santo Domingo, Dominican Republic, have provided the best information currently available, indicating that the main mechanism of action of copper IUDs is prevention of fertilization.



Impact

Copper IUDs, particularly the TCU 380A, are considered the safest and most effective of all the reversible contraceptive methods currently available (WHO, 1994; WHO, 1995; d’Arcangues, 2007). The core information on this subject was produced by HRP. The TCU 380A has become the method of choice of many women for attaining their reproductive goals. The effectiveness and continuation rates of the TCU 380A make it a valuable tool for improving the health status of women. It is estimated that, at present, approximately 160 million women worldwide are using IUDs, in comparison with an estimated



70 million users at the time HRP began its IUD work in the early 1970s. Data on the prevalence of IUD use show a global increment, from 12% in 1984 to 15% in 2004. The increment is particularly noticeable in the Middle East and North Africa, from 9% in 1990 to 16% in 2004. It is reasonable to attribute much of this increment to the comprehensive work conducted by HRP. One person interviewed by telephone said, “HRP rescued the IUD from the American disaster.”

We must recognize the important contributions of other organizations to IUD research and use. The Population Council actually developed the TCU 380A and holds the patent for this product. The Population Council and Family Health International have conducted numerous comparative and introductory clinical trials of copper IUDs in many developing countries. Both organizations have also conducted clinical trials on use of the TCU 380A in particular situations. EngenderHealth played a key role in the introduction of the TCU 380A in many countries. The Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO) and the Center for Communication Programs at Johns Hopkins University designed seminal training and education programmes on IUD use. Finally, a major proportion of the programmes for research, development and introduction of the TCU 380A were sponsored by the United States Agency for International Development. The collective effort of these organizations has contributed to the current level of knowledge and use of the copper IUDs.

Particular areas of impact of the HRP IUD programme are described below.

Long-term effectiveness of copper IUDs

Extended observation of women using two copper IUDs, the TCU 380A and the TCU 220C, in HRP-sponsored trials (WHO 1997b) showed that the cumulative intrauterine pregnancy rates after 12 years of use for the two devices were 1.9 and 7.0 per 100 women, respectively. The low long-term pregnancy rate with the TCU 380A is comparable to that reported in the USA for women who had undergone sterilization. This high level of effectiveness and the 10-year or longer duration of effectiveness make the TCU 380A a valid alternative to female sterilization, without a commitment to a permanent, irreversible method. The initial lifespan of only two years approved by regulatory agencies was progressively increased to the current 10-year duration approved by the United States Food and Drug Administration on the basis of HRP studies. HRP already has data indicating that the TCU 380A is effective for at least 12 years.

One of the interview questions was: ‘What is the duration of the contraceptive effect of the TCU 380A considered to be in your country (< 5, 5–9 or ≥ 10 years)?’. One of the 21 respondents replied < 5 years, nine reported 5–9 years and 11 reported ≥ 10 years. This indicates a discrepancy between the scientific evidence and the knowledge of providers or clients and therefore a need to improve HRP communication strategies or to conduct appropriate translational research. Most of the persons interviewed considered that HRP was highly effective or very effective in disseminating research results, which shows that dissemination is not sufficient to change knowledge or medical practice. One interviewee, who considered that HRP dissemination was effective (mid-point on the five-point scale), suggested that one way of improving dissemination would be to use the Emergency

Contraception Consortium model and possibly establish an IUD Contraception Consortium.

Increasing the duration of IUD use has an important potential global impact. In a comparison of cumulative continuation rates, 63% of women in China and 19% elsewhere still had their IUD at eight years and 47% in China and 13% elsewhere continued use at 10 years (WHO, 1997b). Both in China and elsewhere, large percentages of women continue to use IUDs over long periods.

If women are told that they can keep the same IUD for 10 continuous years, as opposed to having it replaced after five years or less, the average duration of use of the same IUD will be extended. The average duration of use was calculated as the sum of the continuation rates at 1, 2 ... years up to the maximum duration of IUD use that would follow from continuation of the rates cited above. The average duration of use when the maximum recommended duration of use is five years was 3.8 years in China and 2.8 years elsewhere, and the average duration of use when the maximum recommended is 10 years was 6.3 years in China and 3.9 years elsewhere. In China, where the continuation rates are quite high, an increased maximum duration of efficacy has a large impact on the average duration of use. In other parts of the world, where the continuation rates are lower, the average duration of use is increased by a lesser but still significant amount.

An increased average duration of IUD use implies that fewer IUDs and IUD insertions are needed to meet the long-term needs of a given number of IUD users. This implies savings to family planning programmes in terms of commodity costs for IUDs and reduced staff time for insertions. Expulsion and infection are more likely immediately after insertion of an IUD; the number of unintended

pregnancies will be reduced by the smaller number of expulsions, and, to the extent that unintended pregnancies lead to abortions, abortion will be reduced. The case-study authors estimated that, at current levels of IUD use, increasing the maximum time that an IUD remains inserted from five to 10 years would reduce the number of unintended pregnancies by about 68 000 annually. This could in turn reduce the annual number of global abortions by about 43 000. Annex 3 outlines the methods of calculation used.

A reduced number of insertions will also reduce the costs associated with IUD use. Increasing the maximum recommended duration of use from five to 10 years would save more than US\$ 35 million annually in commodity costs to maintain current levels of IUD use. When medical staff time is included in the calculation, the annual savings would be almost US\$ 56 million. Clients would also benefit from the reduced number of insertions: by reducing the number of medical visits, clients could save almost US\$ 60 million annually, as calculated from the reduced costs associated with direct travel costs, travel time and waiting time.

Safety and efficacy of copper IUDs

HRP has produced essential information on the safety and efficacy of the available copper IUDs. Research conducted by HRP and other organizations, such as the Population Council and Family Health International, has shown that the TCu 380A IUD is a safe, highly effective method of contraception. Research on the safety and efficacy of copper IUDs, initiated by HRP in 1972, involving multicentre and multicountry clinical trials in developing countries in all regions of the world, resulted in 156 HRP-supported publications (Annex 2).





Mechanism of action of copper IUDs

One of the original questions addressed by the HRP research programme was the mechanism of the contraceptive effect of copper IUDs. Many programmes were and continue to be negatively affected by the belief that IUDs are abortifacients. HRP-cosponsored studies have shown that the main mechanism of action of copper IUDs is the prevention of fertilization. This information is included in all technical communications, national and international, when the mechanism of action of IUDs is addressed.

One of the questions in the interview was: ‘What is the perceived mechanism of action of the pregnancy prevention effect of the copper-releasing IUDs in your country: prevention of fertilization, prevention of implantation or abortifacient?’ The 21 persons interviewed provided 24 responses because three chose more than one option. Nine responded that the mode of action was prevention of fertilization, 12 said it was prevention of implantation, and three said it was an abortifacient. The limitations of the interview do not permit generalizable conclusions to be drawn; however, 11 of the 12 responses for prevention of implantation came from developing countries; the three responses for abortifacient came from Latin America. This again shows a discrepancy between the scientific information and wrong perceptions at country level. The persistent belief that copper IUDs prevent implantation or are abortifacient is an important reason for the low level of IUD use in certain countries.

Relation between IUD use and pelvic inflammatory disease

The perception that IUD users have a high risk for developing pelvic inflammatory disease persists, and this is considered to be one of the main factors limiting wider use of IUDs in some regions. HRP-produced information showed that the risk for

pelvic inflammatory disease among appropriately screened potential users is actually very low. The overall incidence found in the HRP study was 1.6 per 1000 woman–years, comparable to the incidence in non-IUD users. The rate was 9.7 in the first 20 days after insertion and then declined and remained low and constant subsequently. These findings have been incorporated into guidelines for IUD services.

One of the interview questions was: ‘What is the perception of the risk of pelvic inflammatory disease associated with the use of IUDs in your country?’ Ten of the 21 respondents said that the perception was that the risk was very high or high. Only six respondents said that the perception was that the risk was low or very low. Nineteen of the 21 respondents thought that HRP had contributed significantly to establishing a low risk for pelvic inflammatory disease in appropriately selected women using the IUD. Again, this represents a discrepancy between the scientific evidence and the perception of providers or clients, indicating once more a need to improve communication strategies.

Guidelines for copper IUD use

At the end of the 1990s, HRP/RHR published the *Medical eligibility criteria for contraceptive use* (WHO, 1996), and the *Selected practice recommendations for contraceptive use* (WHO, 1997a), and was working on the *Decision-making tool for family planning clients and providers* (WHO, 2005b) and *Family planning: a global handbook for providers* (WHO, 2007). These publications were the result of consensus reached by groups of experts from all regions of the world. They have been adopted as reference documents for IUD use by all major national and international sexual and reproductive health organizations. They include the current evidence-based guidelines for IUD services. By 2007, the medical eligibility criteria had been introduced into most countries of the world, and

at least 26 national guidelines or norms had been adapted or updated according to the criteria. The criteria have been translated into Arabic, Chinese, French, Laotian, Mongolian, Portuguese (African and Brazilian), Romanian, Russian, Spanish and Vietnamese. One interviewee said: “The medical eligibility criteria is the single most important document, a sea of change.” To a question on the effectiveness of HRP as a source of standards that can be used in shaping international policies and guidelines, 17 of 19 respondents said that it was highly or very effective. One interviewee said: “When WHO speaks, the world listens.” The only person who gave a mildly negative effectivity rating said that “the reason is local obstacles independent of HRP”.

The IUD project in China

In the 1980s, HRP initiated a number of comparative studies in China of the stainless-steel ring, the TCU 220C and the TCU 380A. At that time and in the early 1990s, the stainless-steel ring accounted for an estimated 90% of the IUDs used in China, in spite of the fact that it had a high failure rate. The main reason given for continuing use was the higher production cost of copper IUDs. The study, conducted in 18 centres throughout China, was based on clinical, survey and economic data, and its aim was to compare the costs and benefits of the stainless-steel ring, the TCU 220C and the TCU 380A. HRP conducted a meta-analysis to calculate pregnancy and expulsion rates with 137 602 stainless-steel rings, 8899 TCU 220C and 3021 TCU 380A insertions. The one-year pregnancy rate with the stainless-steel ring was 5.8%, and that with both copper TCU 220C and TCU 380A 1.0%. The one-year average expulsion rate was 11.2% with the stainless-steel ring and 2.0% with the copper TCU 220C and TCU 380A. The five-year continuation rates were 59.6% (stainless-steel ring) and 81% (copper IUDs), respectively.

Another purpose was to provide information to the Chinese Family Planning Commission (now the National Population and Family Planning Commission) on the potential health and economic impacts of changing to copper IUDs. The potential demographic impact of converting from stainless-steel ring to copper IUDs was calculated by comparing the accidental pregnancies that would occur if the 90% use of stainless-steel rings and 10% of copper IUDs were maintained, with the accidental pregnancies that would occur with a switch to exclusive use of copper IUDs over a 10-year period. The results of this analysis are amazing! Over one decade, conversion to copper IUDs would mean a reduction of 28 million pregnancies, 18 million induced abortions, 9 million live births and 790 000 spontaneous abortions and stillbirths. We now know from the present case-study that change did not occur according to these projections, for a number of reasons beyond HRP’s control. The potential impact is nevertheless important, even with partial conversion, and it will increase as the conversion to copper-T IUDs continues.

The potential family savings due to live births averted would have been US\$ 13.02 billion and potential savings for the State US\$ 2.0 billion during the 10 years 1993–2002. The total savings for the State due to induced and spontaneous abortions and stillbirths prevented would have been US\$ 530 million (there are no savings to the family here since the State assumes medical costs associated with these conditions). On the cost side, the additional cost of producing copper IUDs would have been US\$ 35.7 million over the 10-year period, and in the initial years of the conversion when local production was still insufficient to meet needs, copper IUDs bought in the international market would have cost US\$ 31.7 million.





The information provided by HRP encouraged the Chinese family planning programme to discourage use of stainless-steel ring and initiate a change to copper IUDs, namely the TCU 380A. The conversion was started in the early 1990s and is still proceeding, although at a slower pace than originally estimated because of multiple political and economic factors. The experience in China shows that WHO should coordinate with other international agencies or organizations that can influence national development planning.

The methodological approach used by HRP to assess the demographic and economic impacts of decisions made by a family planning programme is a model that could serve other countries. Cost saving is important to policy-makers in developing countries, owing to the scarcity of resources.

The IUD project in Turkey

With the support of HRP, female nurse–midwives in Turkey were trained in a programme set up with HRP technical assistance between 1976 and 1979 to provide IUD services. The numbers of pregnancies, expulsions and removal rates were found to be similar for insertions performed by nurse–midwives and by physicians. The lead investigator, at Hacettepe University, Ankara, had the foresight to involve the Ministry of Health in the project from the onset, and the then Director-General of Family Planning and Maternal and Child Health was a co-investigator in the project. This joint planning and ownership greatly facilitated the dissemination and application of the research results. In 1983, legislation was changed, allowing nurse–midwives to perform IUD insertions and introducing training on IUD use into regular national education programmes. In the 15 years since the law was changed (1983–1998), the prevalence of IUD use increased from 9% to 20%. This experience is included as a case-study of a successful

intervention in the *Turning research into practice* manual published by HRP (Shah, Wright, 2006).

Use of TCU 380A for emergency contraception

In 1997, HRP in collaboration with the National Research Institute for Family Planning in Beijing, China, initiated a study on the safety and efficacy of the TCU 380A for emergency contraception. IUDs were inserted into 1963 women within 5 days of unprotected intercourse; no pregnancies were observed, and no serious adverse experiences or cases of pelvic inflammatory disease were reported after up to one year of use. An important finding was that a high percentage of women continued to use the method. This large study confirmed previous reports that IUDs are a safe and effective method for emergency contraception and are much more effective than hormonal methods. Emergency insertion also resulted in continued use of contraception. These findings support inclusion of the TCU 380A as an option for emergency contraception.

Collaboration between HRP and the International Organization for Standardization

HRP is working with ISO in reviewing the international standard for copper-bearing intrauterine contraceptive devices (ISO-7439). In 2006, HRP conducted a Cochrane review of copper-containing, framed IUDs for contraception, which was published in 2007 (Kulier R, 2006; O'Brien et al., 2008). The aims of the review were to:

- compare the effectiveness and side-effects of different copper IUDs;
- respond to a series of questions raised by members of ISO; and

- support revision of the international standard for IUDs by providing up-to-date evidence that could be used by members of ISO.

On 19–20 September 2006, HRP organized a meeting of the IUD Technical Review Committee at WHO, Geneva. The main purposes were to:

- review the conclusions of the Cochrane systematic review;
- discuss recommended changes to the international IUD standard with members of ISO; and
- discuss preparation of an IUD specification and guidelines for pre-qualification and bulk procurements of IUDs.

The main finding of the Cochrane review was that the TCu 380A was associated with a lower pregnancy rate than the MLCu 375, MLCu 250, TCu 220C or TCu 200 devices. Furthermore, none of the other IUDs reviewed showed any benefit in terms of bleeding, pain or any other reason for discontinuation. On the basis of these findings, the Technical Review Committee presented a number of recommendations on required IUD performance characteristics to ISO, including the requirement that contraceptive effectiveness be determined in a randomized controlled trial with TCu 380A as the control device.

HRP is also preparing a proposed WHO TCu 380A intrauterine contraceptive device specification, following an expert review of the Population Council specification held at WHO, Geneva, on 8–10 August 2007.

ISO is responsible for setting global standards for, among others, the manufacture of mechanical contraceptives. The collaboration between HRP and ISO in preparing or upgrading the international IUD standards is a landmark for HRP, indicating that it is recognized as a highly professional organization

that is in a unique position to make consensus recommendations of the utmost importance in contraceptive technology.

Comment on some possible impact categories included in the case review template

The template includes categories for the evaluation of impact that are addressed in this report. It also asks, however, for information on categories such as contribution to the Millennium Development Goals and poverty reduction. We were unable to obtain any quantitative information on the impact of the IUD programme in these categories, as the necessary indicators were not built into the design of the HRP IUD studies. Furthermore, impact in these areas is not directly contemplated in the HRP mandate. Nevertheless, RHR recently published (WHO, 2006) a document entitled *Accelerating progress towards the attainment of international reproductive health goals*, which includes a comprehensive list of indicators for assessing impact in the five priority areas of sexual and reproductive health adopted by the fifty-seventh World Health Assembly. RHR plans to provide technical assistance to countries for collecting and analysing the data for these indicators. HRP is conducting a study in several Latin American countries to assess the feasibility of obtaining the required information from existing sources, such as demographic and health surveys and other surveys. If the impact in these areas is indeed the responsibility of HRP, changes will have to be made to the general structure of HRP and additional resources will be needed. The commitment to achieve universal access to sexual and reproductive health care by 2015 would indicate a broader role for HRP/RHR. At present, HRP/RHR resources for achieving outcomes at country level, and, more generally, resources to translate outcomes into impact, are limited.





Growth in IUD use

HRP's work has laid the groundwork for increased global use of IUDs by contributing to the demonstration that it is a highly effective, safe, long-acting method. To date, few countries have reached high levels of IUD use. Those in the developing world include China, Cuba, Egypt, Turkey and Viet Nam, in widely different social and geographic contexts. In these countries, either there is no widespread concern about IUDs or the concern has been overcome. No countries in Africa have achieved high levels of use. We decided to conduct an exercise to demonstrate the potential impact of HRP's work, by estimating the effect, on global use of IUDs, of increasing the growth rates of IUD use in countries where it is lagging to the rates observed in countries of high IUD use.

For this exercise, the countries of the developing world were divided into five groups: sub-Saharan Africa, Asia, China, Latin America and the Caribbean and the Middle East including North Africa. Table 2 shows a synthesis of IUD growth rates presented by Amy Pollack and colleagues to the Hewlett Foundation in May 2006 (unpublished report). The averages given are probably high, given that countries with negative or zero growth rates were not included. Sub-Saharan Africa is an interesting category because of its low use of

family planning, very low use of IUDs and relatively low unmet need for limiting family size, based on national surveys. In several countries in Latin America (e.g. Cuba, Ecuador and Mexico), strong growth appears to have begun. In Asia, there is an excellent opportunity for growth in large countries that have not adopted IUDs. The Middle East and North Africa are analysed apart because sterilization is frowned upon in many Muslim nations; IUDs probably represent the best option for limiting family size in these countries.

Table 3 presents projections of the growth of IUD use under a slow-growth regime and under a rapid-growth regime. The slow-growth regime ('current growth' in the table) is derived by applying the average regional IUD growth rates in Table 2 to all countries in the respective regions. The rapid-growth rate is derived by applying the growth rate of the country with the fastest growth in the region. For China, it is assumed that the current fast growth rates will continue. China is treated separately because of its large size, although other countries (e.g. Cuba, Kazakhstan and Uzbekistan) have similarly large percentages of women using IUDs. Their populations are not, however, large enough to skew the results.

In Africa, even if the moderate growth rate in Kenya is applied to all countries, use of IUDs in 2020

Table 2. Average IUD growth rates by region and regional maximum IUD growth rates (percentage point per year for IUD-specific contraceptive prevalence rate) during longest measured period since 1980

Region	Regional average	Regional maximum
Africa	0.00	0.13 (Kenya)
Asia	0.35	1.00 (Uzbekistan)
Latin America and the Caribbean	0.62	0.94 (Peru)
Middle East and North Africa	0.67	1.42 (Egypt)

The growth rates presented were over various lengths of time, depending on when surveys were conducted.

Source: Pollack AE, Ross J, Perkin G. Intrauterine devices in developing countries: opportunities for expanding access and use. Report submitted to the Hewlett Foundation, 26 May 2006.

Table 3. Projections of IUD users at current growth rates and in a rapid-growth regime (thousands of users)

Region	2005		2010		2015		2020	
	Current growth	Rapid growth	Current growth	Rapid growth	Current growth	Rapid growth	Current growth	Rapid growth
Africa	574	574	646	1 404	726	2 432	818	3 697
Asia	23 251	23 251	32 906	48 073	43 796	76 222	56 058	108 077
China	111 659	111 659	128 629	128 629	146 469	146 469	165 217	165 217
Latin America and the Caribbean	5 675	5 675	8 608	9 905	11 900	14 663	15 588	20 003
Middle East and North Africa	9 797	9 797	12 939	15 512	16 570	22 168	20 761	29 904
Developing countries	150 956	150 956	183 728	203 522	219 462	261 954	258 442	326 899



would increase sixfold from current use (from 574 000 to 3 697 000). In both Asia and Latin America, where IUDs have been more widely accepted, the potential growth is fourfold relative to current use. In the Middle East and North Africa, where use of IUDs is already relatively high in several countries, the growth would be threefold.

An alternative way of looking at the table is to compare the scenarios in 2020. In Africa, a rapid-growth scenario, which is actually slower than in other regions, would yield four times as many users as the current growth rate. In Asia, the differential

in 2020 would be twice as many for the rapid-growth scenario. In Latin America and the Middle East, where IUD use is already being taken up, the difference would be 50% higher in the rapid-growth scenario.

The rapid growth in IUD use should result in reduced numbers of pregnancies. Given that women using IUDs are highly motivated to limit their number of births, reduced numbers of pregnancies also imply a reduced number of abortions. Table 4 shows estimates of averted pregnancies and averted abortions. The numbers of

Table 4. Projections of averted pregnancies and abortions as a result of rapid growth of IUD use (in thousands)

Region	2005		2010		2015		2020	
	Pregnancies	Abortions	Pregnancies	Abortions	Pregnancies	Abortions	Pregnancies	Abortions
Africa	0	0	55	26	123	58	207	97
Asia	0	0	1 092	513	2 335	1 097	3 745	1 760
China	0	0	0	0	0	0	0	0
Latin America and the Caribbean	0	0	93	44	199	93	318	149
Middle East and North Africa	0	0	185	87	403	189	658	309
Global	0	0	1 425	670	3 059	1 438	4 929	2 317



averted pregnancies were estimated by multiplying the difference in the numbers of IUD users by the difference in pregnancy rates with a modern method such as pills (pregnancy rate of eight in the first year of use as commonly used) and with copper-bearing IUDs (0.8 pregnancy rate in the first year) (WHO, 2007). The numbers of abortions averted was estimated by multiplying the number of pregnancies averted by the probability that pregnancies resulting from contraceptive failure end in abortion. Sedgh et al. (2007) cite Wang and Altmann (2002) as reporting that, in China, 70% of contraceptive failures result in abortions. Gold (1990) reports that 47% of unintended pregnancies in the USA end in abortion.

Cost-effectiveness

Two cases illustrate the cost-effectiveness of the IUD research conducted by HRP. First, in 1990, HRP was conducting research on the long-term safety and efficacy of TCu 380A, TCu 220C and Multiload 375; the safety and efficacy of the new frameless IUD; and an implantable post-placental IUD. These studies were being conducted in 15 countries (12 developing countries), with the participation of 45 scientists. The total expenditure for that year was US\$ 78 000. Second, the total cost of the two-year comparative trials of the IUDs being used in China, conducted to identify the safest and most effective IUD, was US\$ 59 485. These costs are many times less than those of similar trials conducted by other organizations.

Several factors explain these low costs:

- The principal investigators and most of the research support staff did not receive any compensation.
 - The members of research review groups, steering committees and task forces did not receive any compensation.
 - The trials were conducted with existing local infrastructure, supported by national academic or public sector institutions.
 - The trials were conducted at sites where other HRP-supported trials were being conducted, and many of the sites received independent support from the institutional strengthening component of HRP.
 - Monitoring of the sites was limited (but data collection problems were frequent as a result).
 - All the studies were designed, initiated and conducted before the current requirements of good clinical practice and research ethics review committees were in place.
 - National regulatory agencies had limited involvement and limited requirements.
- It is doubtful that the same degree of cost-effectiveness can be maintained in the future. The investigators and members of HRP scientific groups will continue providing their work without expecting any monetary compensation, as they are proud of their participation in HRP research. There are, however, other factors:
- HRP does not conduct the same volume of research on IUDs (or other topics) as in the past. Furthermore, support for institutional strengthening has diminished. As a result, the budgetary needs of the sites have increased.
 - The cost of conducting high-quality IUD clinical trials has increased substantially over the past few years. The stringent, and no doubt necessary, requirements of good clinical practice, research ethics committees and national regulatory agencies have increased the costs of conducting clinical trials worldwide.

- The difference in the cost of conducting similar, high-quality clinical trials of IUDs that comply with the same requirements should not be large. The difference in costs between HRP and other public sector research organizations should be moderate.

Conducting IUD research with HRP should not be seen as only a cost-saving advantage to the sponsors. HRP has important advantages over other research organizations, including:

- a large network of research sites and collaborators, created while conducting the IUD trials, which is unique in the world;
- direct, close collegial relations with local and national institutions, which facilitate the conduct and public health impact of IUD studies;
- a structure and prestige that make it the ideal coordinating or leading centre in collaborative multinational research on IUDs;
- the high quality and influence of research conducted by HRP; and
- “It has the best name in the business.”

Future

The 21 persons interviewed were asked, ‘What type of IUD research should receive more attention in the future?’, with a choice of six general research areas: mechanism of action; safety (name subject); effectiveness and duration; communication, advocacy and information; programme research; HIV/sexually transmitted infections; and other (name subject). The interviewee was asked to classify each area as high-, medium- or low-priority. Some of the 10 persons interviewed by e-mail did not classify all the areas, so, for most areas, 21 responses were not obtained. The three areas that were considered as high priorities were: HIV/sexually transmitted

infections (15 persons), communication, advocacy and information (14 persons), and programme research (13 persons). The area of HIV/sexually transmitted infections received only two low classifications, and communication, advocacy and information and programme research received only one low classification each. Mechanism of action, effectiveness and duration and safety received high priority ratings by seven, six and two persons, respectively. Conversely, these areas received a low priority rating by eight, seven and 10 persons, respectively. Some comments in the personal or telephone interviews were: “We know what we need to know about the safety and effectiveness of IUDs”; “The resources could be better used in other areas”; “The persisting questions on the mechanism of action of IUDs are theological, not scientific”.

No direct questions on research on hormone-releasing IUDs were included in the questionnaire; however, six persons in the personal or telephone interviews, when asked if they wanted to mention another area, cited development of a generic levonorgestrel-releasing IUD for the public sector as a high priority. Interestingly, four of these six persons were also the four interviewees who were high-level officials in other international organizations involved in sexual and reproductive health.

The question on future research priorities was also posed at a session with HRP staff responsible for the IUD programme. The areas mentioned as being of high priority, in the following rank order, were development of a generic levonorgestrel-releasing IUD, programme research, communication, advocacy and information, and HIV/sexually transmitted infections. The HRP staff noted that new resources would be needed to conduct research in these areas.





The personal and telephone interviews showed strong concern about the discrepancy between the available scientific evidence and persistent wrong perceptions and medical barriers to IUD use. It is important to determine why, if the IUD has so many advantages for women and programmes, it remains insufficiently used. This concern became apparent when communication and programme research were discussed. It was stressed that scientific evidence is needed on why IUDs are used in some countries or by some women and not others. This concern extends to the general problem of improving the translation of HRP outcomes into impact.

other international organizations interested in improving IUD use should be strengthened.

- Programme activities and related research should be designed and supported to overcome the persistent barriers to IUD use.
- Research on the interrelations between IUD use and HIV/sexually transmitted infections should be supported.
- Research on a generic levonorgestrel-releasing IUD should be supported.

Recommendations

- The ‘research into practice’ strategy of RHR should be strengthened and updated. A persistent discrepancy continues to exist between the scientific information produced by HRP and the knowledge, attitudes and practices of policy-makers, service providers and the public on important issues that continue to limit the use of IUDs.
- The level of impact in the IUD area for which HRP is responsible should be clearly defined, and the appropriate indicators should be identified and considered in the design of all research projects. To this end, important structural changes and additional resources might be necessary.
- The presence of HRP staff at country level should be increased to allow them participate in planning and overseeing local strategies for introducing the results of IUD research into programmes and services.
- Collaboration between HRP and WHO country offices, local policy-makers and

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Annex 1. HRP-supported research on IUDs, 1972–2007



Randomized controlled clinical trials (multicentre, multi-country, worldwide, unless otherwise specified)

- Progesterone-releasing (65 µg/day) IUD (Alza-T) vs 'plain' IUD
- Progesterone-releasing (65 µg/day) IUD (Alza-T) vs Cu 7 (South America)
- Lippes loop vs Cu 7 vs TCU 220C for insertion after therapeutic termination of pregnancy
- Lippes loop vs Cu 7 vs TCU 220C for insertion after spontaneous abortion
- Lippes loop vs Cu 7 vs TCU 220C for interval insertion (multiparous women)
- Lippes D loop vs Cu 7 vs new postpartum CuT from Population Council, for post-placental insertion; discontinued in 1977; restarted with long inserter tube and Multiload Cu 200 instead of Lippes loop, which resulted in more bleeding and expulsion than other devices
- TCU 220C, Multiload 250 and progesterone-releasing IUD IPCS-52 (same as Alza-T; device discontinued in 1982 but study continued with two arms) for interval insertion and for insertion after therapeutic termination of pregnancy
- TCU 220C vs Lippes loop (Tunis)
- TCU 220C and progesterone-releasing IUD IPCS-52 (same as Alza-T; device discontinued in 1982) for interval insertion
- TCU 220C and TCU 380A for interval insertion (Shanghai V added to randomized clinical trial in Shanghai only)
- TCU 220C vs Lippes loop (Cali)
- TCU 220C vs TCU 200 (Hanoi)
- TCU 220C vs Shanghai V vs stainless-steel ring (Beijing)
- TCU 220C, Nova T and the WHO 2 µg levonorgestrel-releasing IUD (device discontinued in 1984)
- Nova T vs Cu 7 (Shanghai)
- TCU 380A and Multiload 375
- Flexigard vs TCU 380A
- Mirena vs TCU 380A
- TCU 220C, TCU 380A and Chinese uterine-shaped copper ring (UCD-300) (13 centres in China)
- TCU 380A vs Multiload 375 (Ho Chi Minh City)
- TCU 380A vs TCU 220C for interval insertion (Zambia)

Non-randomized clinical trials

- TCU 220C (Shanghai)
- Mahua ring (Tianjin)
- TCU 380A (five centres in Viet Nam)
- TCU 380A (Ulaan Bataar)
- comparative study of clinical performance and users' satisfaction with three methods (IUD, pill, medroxyprogesterone acetate)
- TCU 380A for emergency contraception (18 centres in China)
- post-marketing surveillance of Norplant: a concurrent cohort study in which one of the cohorts was a group of 6625 Cu IUD users who provided information on the safety and efficacy of IUD use

Studies of menstrual blood loss

Comparative studies in Beijing, Juis de Fora, London, Los Angeles, Lusaka, Mexico City, Santiago, Seoul, Shanghai, Stockholm and Tokyo:

- progesterone-releasing (65 µg/day) IUD (Alza-T)

- Lippes loop
- Cu 7
- TCu 220C
- IPCS-52 (Alza-T)
- Shanghai V
- stainless-steel ring
- Chinese ring (two studies)
- Nova T
- 2 µg levonorgestrel
- Flexigard

Studies of agents to treat IUD-induced endometrial bleeding

- Effectiveness of intrauterine administration of antifibrinolytic agent to decrease IUD-induced bleeding
- Evaluation of aromatic diamidines and prostaglandin synthetase inhibitors for possible incorporation into IUDs to decrease menstrual blood loss
- Evaluation of heparin antagonist to reduce menstrual blood loss

Studies of mechanism of action of IUDs

- Study of prostaglandin production by endo- and myometrium in users with and without IUD-induced pain
- Launch of multicentre investigation into the mechanisms of IUD-induced bleeding in Colombia, Ireland, Mexico, Netherlands, Sweden, United Kingdom, USA
- Study of effect of progesterone-releasing (65 µg/day) IUD (Alza-T) on endometrial biochemistry and morphology
- Study of microbiology and histology of fallopian tubes in IUD users (Lippes loop, Saf-T-coil,

TCu 200, TCu 220C, Cu 7) in Bangkok (two studies), Cali, Dunedin, Halifax, Havana, London, Los Angeles, Montreal, Santiago, Seoul, Sheffield and Singapore



Studies for development of new devices

- Phase I study of chloroquine-releasing IUD
- Phase I study of effect of norethisterone-releasing (10 µg/day) and levonorgestrel-releasing (8 and 2 µg/day) IUDs on menstrual blood loss and on endometrial morphology
- Measurement of uterine cavity dimensions during first eight days postpartum (London)
- Development and testing of a device to measure the uterine cavity
- Ultrasound studies of the IUD involving uterus postpartum
- Investigation of biodegradable polymers to be added to IUDs for postpartum use
- CuFix PP330 for post-placental insertion (six centres)

Studies of IUD safety

- Laparoscopic study of cases of suspected pelvic inflammatory disease (Sweden)
- Case-control study of pelvic inflammatory disease and ectopic pregnancy (12 centres)
- Analysis of data from 12 randomized clinical trials and one non-randomized pilot study, showing that the risk for pelvic inflammatory disease is highest during the first 20 days after insertion

Study of public health impact

- Public health effect of switching from steel rings to Cu T IUDs in China

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Annex 3. Potential effects of increasing the maximum recommended duration of IUD use



Increasing the duration of recommended IUD use could have important global impacts. Extending the maximum time that an IUD remains inserted has potential benefits in terms of reducing morbidity from unsafe abortions, reducing the number of unintended pregnancies, reducing the financial burden to health systems and providing financial benefits to women in terms of less time spent on visits for IUD insertion. As the risk for IUD expulsion is greatest in the period immediately following insertion, reducing the number of IUD insertions will reduce the incidence of expulsions. Frequently, women do not notice an IUD expulsion or partial expulsion and are therefore at particular risk for pregnancy. If a woman becomes pregnant unwillingly, she is very likely to have an abortion, which in the developing world is often unsafe.

We estimated the impacts by extrapolating from the number of insertions that are necessary to maintain current global use of IUDs under two scenarios of IUD use: a maximum duration of IUD use of 5 years and a maximum duration of IUD use of 10 years.

The general approach for estimating the reduced number of insertions is flow analysis. Over time, even if there is no growth in IUD use, women who discontinue use must be replaced by new users, women who use their IUD for the recommended maximum duration must have their IUD replaced, and women who reach menopause must be replaced by new users. The last is perhaps more of a statistical than a programme issue, as these women do not necessarily stop using IUDs; however, most surveys of IUD use confine their samples to women who are either 15–49 or 15–44 years of age. In this approach, discontinuation rates have a direct impact on the number of new users needed to maintain a constant IUD prevalence rate. The discontinuation rate due to all causes also

has an effect, through the percentage of women who remain continuous users until the end of the recommended life of an IUD.

The number of insertions required is estimated for each country (United Nations, 2006) by summing the number of insertions needed to replace IUD users who reach menopause, IUD insertions for women replacing those who discontinue use and IUD insertions needed because the IUD has reached the recommended duration. In addition, the following calculations are made country by country and then summed for a global total:

- number of expulsions = number of insertions × probability of expulsion
- number of unintended pregnancies = number of expulsions × probability that a pregnancy will follow from an expulsion
- number of abortions = number of unintended pregnancies × probability that an unintended pregnancy will be aborted
- number of unsafe abortions = number of abortions × probability that an abortion is unsafe
- medical expenditures = number of insertions × unit costs
- value of women's time for IUD insertion = number of insertions × time for women to have IUD insertion × imputed value of time

Many of the parameters are country- or region-specific, such as the number of IUD users, gross national income per capita and percentage of abortions that are unsafe. The values used for several of these parameters are as follows:

- risk for expulsion in first year (UNFPA, 1992): 0.02

- probability of pregnancy after an expulsion (UNFPA, 1992): 0.273 (this is probably an underestimate, as women were carefully monitored in the clinical trial; expulsions were more quickly detected than would be likely under field conditions)
- probability of abortion if pregnancy occurs while using an IUD (abortions per IUD failure): 0.70 in China (Wang, Altmann, 2002; Sedgh et al., 2007); 0.47 in the rest of the world (Gold, 1990, for the USA, therefore probably too low)
- percentage of abortions that are unsafe (Sedgh et al., 2007): calculated regional averages
- commodity and drug costs of IUDs (Vlassof et al., 2004; costs presented do not include overheads or indirect costs; 2001 US\$ converted to 2006 US\$ with deflators from the World Bank Development Indicators Database, accessed 22 February 2008): US\$ 2.84
- staff costs (Vlassof et al., 2004; 2001 US\$ converted to 2006 US\$ with deflators from the World Bank Development Indicators Database accessed 22 February 2008): US\$ 1.66
- patient time to obtain IUD (days; based on two medical visits, one for insertion and one for follow-up, each visit requiring 30 min of travel time, 30 min of waiting and 30 min for the service): 0.375
- imputed value of patient's time (World Bank Development Indicators Online accessed 5 December 2007; current US\$): annual gross national income per capita / 260 days (using country-specific values)

Table A1 presents a global estimate of the effect of increased duration of IUD use. The first two columns show a comparison of the various estimates for a two-year period of insertion and a five-year period of insertion. The third column

is the difference between the two or the effect of increased duration of insertion.

The number of IUD insertions would be reduced by 12 million if the maximum recommended duration of IUD use increased from 5 to 10 years. About 68 000 unintended pregnancies and 43 000 abortions could be averted annually. The number of averted unsafe abortions would be relatively small, at 4000, because most of the IUD use in the world is concentrated in China where abortion is generally safe. The authors also estimated the number of averted deaths on the basis of international estimates of mortality from unsafe abortion, which would be less than 10. The number of unintended pregnancies and associated abortions is relatively small because even after discounting for the fact that expulsions are more likely near the time of insertion, IUDs are still a very effective method of contraception.

The financial savings to the health system could be large. The estimates presented here show potential savings of more than US\$ 35 million on drugs and IUDs and US\$ 21 million on staff time. The savings to women in terms of the opportunity costs of their time would be almost US\$ 60 million annually.

China accounts for about 70% of global IUD use and therefore has an important influence on the aggregate global results. Table A2 therefore replicates the results of Table A1 for China only. Table A3 replicates the results in Table A1 excluding China.



**Table A1. Estimates of potential global effects of increased duration of IUD use (in thousands)**

Effect	Maximum recommended duration of use (years)		Difference or effect of increased maximum duration of use
	5	10	
Number of IUD users	159 687	159 687	–
Number of insertions to maintain current usage	44 794	32 379	12 415
Annual expulsions	896	648	248
Number of unintended pregnancies	245	177	68
Number of abortions	154	112	43
Number of unsafe abortions	15	11	4
Expenditures for commodities and drugs (2001 US\$)	127 355	92 057	35 298
Expenditures for staff time (2001 US\$)	74 375	53 761	20 614
Total medical costs (2001 US\$)	201 731	145 819	55 912
Value of women's time for IUD insertion (2006 US\$)	214 028	154 387	59 641

Table A2. Estimates of the potential effects of increased duration of IUD use in China (in thousands)

Effect	Maximum recommended duration of use (years)		Difference or effect of increased maximum duration of use
	5	10	
Number of IUD users	111 601	111 601	–
Number of insertions to maintain current usage	31 408	22 743	8666
Annual expulsions	628	455	173
Number of unintended pregnancies	171	124	47
Number of abortions	120	87	33
Number of unsafe abortions	–	–	–
Expenditures for commodities and drugs (2001 US\$)	89 298	64 661	24 637
Expenditures for staff time (2001 US\$)	52 150	37 762	14 388
Total medical costs (2001 US\$)	141 448	102 423	39 026
Value of women's time for IUD insertion (2006 US\$)	91 054	65 932	25 122

Table A3. Estimates of the global potential effects of increased duration of IUD use, excluding China (in thousands)

Effect	Maximum recommended duration of use (years)		Difference or effect of increased maximum duration of use
	5	10	
Number of IUD users	48 086	48 086	–
Number of insertions to maintain current usage	13 386	9 636	3 750
Annual expulsions	268	193	75
Number of unintended pregnancies	73	53	20
Number of abortions	34	25	10
Number of unsafe abortions	15	11	4
Expenditures for commodities and drugs (2001 US\$)	38 057	27 396	10 661
Expenditures for staff time (2001 US\$)	22 225	15 999	6 226
Total medical costs (2001 US\$)	60 282	43 396	16 887
Value of women's time for IUD insertion (2006 US\$)	122 974	88 454	34 519



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