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Launched by the World Health Organization in 1972, the UNDP/ UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction is a global programme of technical cooperation. It promotes, coordinates, supports, conducts, and evaluates research on human reproduction, with particular reference to the needs of developing countries.

Expanding contraceptive options through their systematic introduction

If women and men are given more contraceptive choices than those available to them now, then more couples are likely to find a method that suits their needs at different stages of their reproductive lives. However, experience shows that when a new method is introduced into a family planning programme without regard for such things as the capability of the services to deliver another method and its potential acceptability to the users, the new method may fail to realize its full potential in terms of prevalence and user satisfaction.

In 1991 the Programme broadened its research activities to include research on the introduction and management of new or underused methods of fertility regulation into family planning programmes. This research aims to help governments and family planning agencies in optimizing the use of fertility regulation technologies and in broadening contraceptive options. An essential feature of increasing contraceptive options is that users should be able to make an informed choice between the different family planning methods. The methods must have been adequately tested for safety and efficacy and should be of the highest quality and affordable in price.

The objectives of the Programme in the area of introduction and management of contraceptives are:

(*a*) generation and dissemination of information necessary for the addition of new or underused methods of fertility regulation into family planning programmes, particularly through the conduct of a systematic introductory process;

(*b*) determination of service delivery and user needs and identification of the management skills and practices necessary to ensure appropriate quality of care in the introduction of a method;

(*c*) facilitation, through research on product management and establishment of standards and guidelines, of the transfer of contraceptive technologies including registration, production and sustainability of these methods, and the understanding of economic implications of their introduction; and

(d) development of methodologies for a systematic introductory process.

Initially, the Programme focused its introductory research on the once-a-month injectable contraceptive Cyclofem, which was developed by the Programme. This research was carried out to evaluate whether, under more routine service conditions, the use-effectiveness and reasons for discontinuation of the method were similar to findings in earlier clinical studies of safety and efficacy.

This issue of *Progress* presents a new three-stage strategy for the introduction of methods. There is also an article on the Concept Foundation—a non-profit body created to transfer health technologies to developing countries. Finally, this issue also discusses the conclusions of a group of experts on the introduction of Cyclofem and Mesigyna into family planning programmes.

INSIDE

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A three-stage approach to the introduction of contraceptives into family planning programmes

Progress
in Human Reproduction Research

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Research on the introduction of contraceptives into family planning programmes is conducted by the Programme's Task Force on Research on Introduction and Transfer of Technologies for Fertility Regulation. Established in 1991, this Task Force is a joint activity between the Programme and the WHO Division of Family Health.

The Task Force initially focused its research on the introduction of the once-a-month injectable contraceptive Cyclofem in developing countries. The introduction strategy employed by the Programme was based largely on that used by the Population Council in the introduction of Norplant. However, in the past two years the Task Force has evaluated the lessons learnt from this product-driven approach and used them to develop a new strategy for the introductory process. One of the most important lessons has been that although method-specific approaches are useful in identifying certain programmatic implications of introducing another method, they do not necessarily help family planning programmes in evaluating the ability of the services to provide the new methods with appropriate quality of care under routine delivery conditions.

Thus, the new research strategy, which is now being implemented, focuses mainly on users' needs for additional methods and the capability of the services to provide the appropriate quality of care required for the delivery of methods. It addresses the interfaces between the users, the service delivery system, and the technology, as shown in Fig. 1. It is both intentional and significant that "users" appear at the apex of the triangle, and not technology. Furthermore, it is a country-based strategy which involves collaboration in both research and decision-making. It is initiated, implemented, and controlled by policy-makers (in for example the Ministry of Health) and the staff of the national family planning programme, but with the full involvement of the spectrum of stakeholders, including: biomedical, health management, and social science researchers; service providers; and women's health advocates and consumer groups. The strategy comprises three stages: Stage I—the assessment of user and programme needs; Stage II—service-delivery and introductory research; and Stage III—the use of the findings of the research for decision-making, policy, and planning. The three stages are summarized in Fig. 2.

The question may be asked, why one should go through such a systematic process which may take over two years to complete? Why cannot providers simply be trained and given counselling materials and supplies be made available? There are sufficient lessons which suggest that without a systematic approach to introduction, expensive mistakes may be made which may be difficult to correct later. For example, a method may earn a bad name and a persistent negative image. A significant initial investment is essential for the long-term viability of a method. Moreover, the appropriate introduction of a new or underutilized technology also provides an opportunity to improve quality of care not only for the new technology but also for the existing methods. There is a general tendency for technical standards and counselling procedures to deteriorate as familiarity with a method increases, unless conscious steps are taken to maintain them. The introductory process can help bring the overall quality of care to an appropriate level.

Apart from focusing on user needs and service capabilities, there are other considerations which must be addressed within the strategy. For example, it must address product

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management, which includes all those issues which together allow the sustainable supply of appropriate products in a satisfactory condition to the point at which they are obtained by the user. They include the appropriate selection and subsequent procurement of products, product monitoring and control from receipt to use, quality control at all points of the distribution chain, distribution and logistics management and, if appropriate, local manufacture. The introduction of a method should not be explored in a country which is unable to manage the product nor should networks for distribution and logistics be developed if a Stage I assessment indicates an unfavourable service environment or lack of demand.

Another important area for consideration within the strategy is the economics of the whole process. This includes an assessment of commodity and service delivery costs of existing and proposed methods at Stage I and subsequent research at Stage II on the cost implications of the method being introduced.

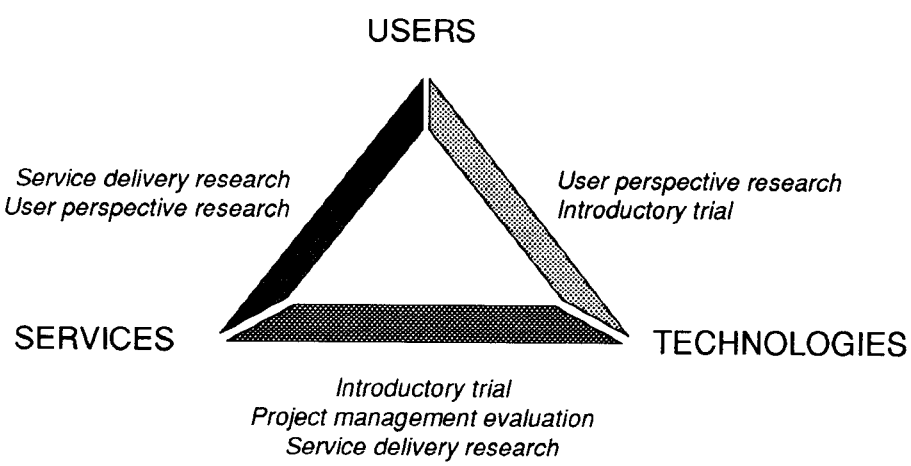
Stage I: Assessment

Stage I comprises an assessment of the current status of the family planning programme, the method mix it offers, its coverage and service delivery infrastructure. Here the aim is to assist the programme in determining the potential usefulness of adding new methods or expanding the use of underutilized methods, and how the service system will cope with the addition of new methods.

The Stage I assessment is undertaken through: (*a*) a limited observation of service delivery practices; (*b*) interview of stakeholders; and (*c*) review of secondary data. At this stage observation of service delivery practices is limited, but is organized to provide an initial impression of the family planning services at the primary, secondary, and tertiary health care levels. Informal interviews are conducted at the clinic level with both users and providers. Interviews are also scheduled with representatives of various health advocacy groups, opinion leaders at different levels of the society, researchers, programme managers, and policy-makers. Secondary data sources are used for information on current method mix, public and private sector use of family planning, contraceptive use patterns and prevalence, socioeconomic factors, age-group distribution and method use, and sociocultural practices as they may affect contraceptive selection. Certain other issues should also be reviewed, such as: policies on contraception and abortion; factors influencing the purchasing decisions (marketing strategies, donor agency policies); regulatory, logistics and distribution systems; structure of the public sector programme for the provision of services; and role of the private sector.

The new research strategy focuses mainly on users' needs for additional methods and the capability of the services to deliver those methods with appropriate quality of care.

Fig. 1. Interfaces between users, services, and technologies



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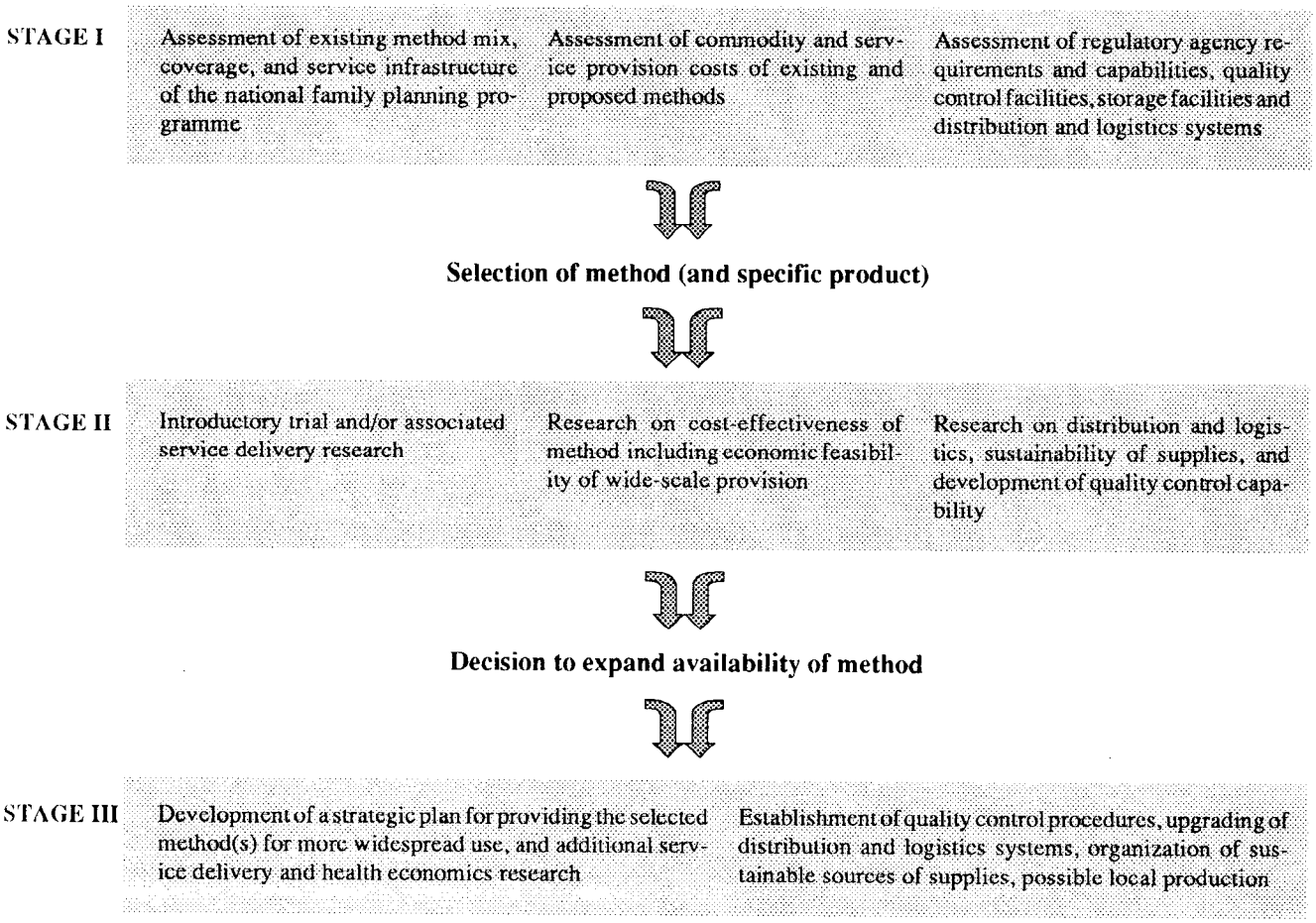
The introduction of a method must address product management issues which will allow the sustainable supply of products in an acceptable condition to all delivery points at which they are needed.

Including the planning process, the assessment will take up to three months and should be followed by a workshop at which the results of the assessment are discussed in relation to user and programme needs. Possible outcomes of Stage I assessment could be: (*a*) that Stage II research on a particular new method should be started; (*b*) a particular new method should not be considered for introduction into the programme; (*c*) an existing but underutilized method could fulfil a need and should be investigated; or (*d*) a method in the current method mix should be discontinued.

Stage II: Introductory research

Once a decision is made to introduce a new or underutilized method, research projects are designed to examine: (*a*) the system of supply (issues affecting the service delivery system's ability to provide services); and (*b*) the system of demand (user perspectives regarding the service system and on the specific contraceptive technology). A variety of research methodologies are used to conduct such research. However, a major part of the research should cover: (*a*) service delivery issues, particularly on the management of services; (*b*) the provider–user interface; and (*c*) factors influencing the supply of the method. Stage II evaluates the quality of care in the context of policy, organization, and management of the services, and suggests what changes would be necessary when the chosen method is introduced. If the technology is of a familiar nature, the service–technology and user–technology interfaces may not have to be researched through introductory trials. Under this strategy the introductory trial—which is a more clinic-based activity focused on safety, efficacy, continuation rates, and reasons for discontinuation—

Fig. 2. Activities at different stages of the introductory process and the decisions required before proceeding from one stage to the other.



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need be undertaken only when an unfamiliar technology is being introduced. Then there would be a need for a fuller programmatic evaluation prior to introduction and registration.

Stage III: Expansion of availability

The purpose of Stage III is to apply research findings to policy development and planning. Based on evaluation of the Stage II research, decisions are made whether it is appropriate to expand use of the method to a larger scale and, if so, develop a strategic plan for providing the method throughout a programme. It may be that additional service delivery and product management issues are identified in the scaling-up process and specific research projects are undertaken to assess them.

Other issues

While the strategy addresses the identification of a method for introduction and follows a systematic approach to making it more widely available through the most appropriate public or private sector channels, it also can be used when a method has already been identified. For example, a Government may wish to replace an existing product with a modern version. In China, a decision has been taken to replace the stainless steel ring used for intrauterine contraception with a modern copper-bearing device (see *Progress* No. 27, 1993). Thus, this would go into Stage II of the research process. Similarly various women's organizations have identified the need for user-controlled barrier methods and, as such, the re-introduction of the diaphragm could be considered in certain programmes through Stage II research.

The strategy addresses the identification of a method for introduction and follows a systematic approach to making it more widely available through the most appropriate public or private sector channels.

Introductory trials of Cyclofem

Up till now most of the Stage II activities of the Task Force on Research on Introduction and Transfer of Technologies for Fertility Regulation have focused on work begun previously on the introduction of Cyclofem—a once-a-month injectable contraceptive developed by the Programme. These trials were carried out to evaluate whether, under more routine service conditions, the use-effectiveness and reasons for discontinuation of the method were similar to findings in earlier clinical studies of safety and efficacy. The trials have been completed in Indonesia, Jamaica, Mexico, Thailand, and Tunisia. More than 9000 women were recruited into these studies at urban and semiurban, primary or secondary health care centres, and more than 70 000 woman–months of experience was accumulated.

The results of these trials were very reassuring. For example, the trials established that even under routine service conditions the efficacy of the method was high, with a cumulative 12-month life-table pregnancy rate of less than 0.1% per 100 woman–years.

Reasons for discontinuation from the study varied greatly between the five countries. The Phase III clinical trial had shown a major difference between centres in discontinuation rates for bleeding-related reasons and amenorrhoea. Similar differences were reflected in the introductory trial, where a large range of discontinuation rates was observed for bleeding-related reasons, from 1.4% in Indonesia to 24.8% in Tunisia.

Personal reasons for discontinuation included those reasons which were not due directly to method-attributable side-effects. These provide important clues to managing the introduction of the method more efficiently. A woman's reason to discontinue for personal reasons may be influenced by other users or members of the community, or may reflect the subject's treatment or perception of treatment by service staff, or the inconvenience of the services. Discontinuations for personal reasons were greater than seen in Phase III trials. They included "inconvenience and timing", "moved away", "desire for pregnancy", and, in the case of Thailand, "no further need" and "change of method". In Tunisia, "negative perceptions" on the part of both users and providers was also included as a reason.

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The Concept Foundation—linking the public and private sectors

Although the Concept Foundation is closely associated with the public sector, it works with companies to assure reasonable profits, for it believes that only through competitive return on investment would it be possible to mobilize the private sector.

When the Programme began its contraceptive development activities it was expected that industry would take over the production, marketing, and other introduction activities, once publicly funded clinical trials had been completed. However, because of the uncertainties of public sector markets and of liability associated with contraceptives, international pharmaceutical companies have not shown much interest in taking over public sector products. Thus, it was felt that a non-profit mechanism was needed to undertake these types of activity. The Concept Foundation was created in 1992 by the Program for Appropriate Technology in Health with assistance from the Programme, specifically with these objectives in mind .

Located in Bangkok, Thailand, the Foundation facilitates the transfer of manufacturing technology, providing technical assistance and independent quality assurance, undertaking selection of suitable manufacturers and distributors, arranging license agreements, and ensuring that liability issues are addressed. An important objective of the Foundation is to ensure that products are of the highest quality and sold at the lowest possible price. The Foundation has been supporting the transfer of technology related to the production of the once-a-month injectable, Cyclofem, in Indonesia, Mexico, and Thailand. Manufacturers in Indonesia and Mexico have already registered the product in their respective countries and begun its marketing.

There are several advantages for pharmaceutical companies in developing countries to work with the Concept Foundation. First, the products made available by the Foundation emanate from highly regarded public sector research institutions, such as the Programme. Second, the Foundation is able to provide the technical assistance needed for production and marketing, especially for export markets and for public sector use. Third, it can help in obtaining financing on favourable terms. Finally, although the Foundation is closely associated with the public sector, it works with companies to assure reasonable profits. The Foundation believes that only through competitive return on investment would it be possible to mobilize the private sector.

The Foundation is addressing a major need in assuring that products developed to address major health problems in developing countries are produced and distributed at affordable prices. Although potential markets for these products are huge, the inability of many people in developing countries to pay commercial prices renders such products unattractive to multinational pharmaceutical companies. The novel approach to marketing adopted by the Concept Foundation can help to make the much needed health products available to all.

As mentioned above, the Concept Foundation is likely to deal mainly with products developed by institutions such as the Programme, which for lack of sufficient resources or appropriate mandate cannot undertake commercial manufacture and distribution. However, it is anticipated that there may be instances where products developed by commercial companies are made available through the Concept Foundation. These are likely to be products that the developers do not want to market because they perceive them not to yield sufficient profit.

The Programme believes that even though at the time when the Concept Foundation was established its approach to the transfer of technology and intellectual property was regarded as experimental and untested, it is now certain that without the Foundation it would have been difficult to make the Programme's once-a-month injectable contraceptive, Cyclofem, available to so many people in so many countries so quickly.

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Experts recommend introduction of Cyclofem and Mesigyna into family planning programmes

On 1–3 June 1993 the Programme organized a meeting of experts to review the available data on once-a-month injectable contraceptives. The experts concluded that the two once-a-month injectables developed by the Programme, namely Cyclofem and Mesigyna, are safe and effective for fertility regulation and can be added to the existing range of methods.

Injectable contraceptives have been in use for over 20 years. The first methods to become available contained only one hormone, a progestogen. These were the three-monthly preparation depot-medroxyprogesterone acetate (DMPA), currently used by over 9 million women, and the two-monthly preparation norethisterone enantate (NET-EN), which is used by over one million women worldwide. Both are highly effective but induce marked irregularities in menstrual bleeding patterns. Although these have not been shown to have adverse health effects, many women find the irregularity of menses unacceptable.

To offer an alternative to women, and knowing that the combination of an estrogen with a progestogen could overcome the problem of irregularity of bleeding, researchers tested the combined approach. This resulted in two such methods becoming available: one in Latin America, and another in China. Since concerns were raised about the safety and efficacy of these methods, the Programme worked on two alternative preparations, namely Cyclofem and Mesigyna.

Cyclofem contains 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate (an estrogen), and Mesigyna contains 50 mg of NET-EN and 5 mg of estradiol valerate (an estrogen). These preparations have proved to be highly effective. In Phase III WHO clinical trials the pregnancy rate at 12 months of use for Cyclofem was 0.2% or less, and that for Mesigyna 0.4% or less. These figures for efficacy are similar to those recorded in Phase III WHO studies with the progestogen-only injectables, DMPA and NET-EN.

In women using DMPA, regular bleeding patterns were never seen in more than 9% of the women. But with Cyclofem and Mesigyna about two-thirds of the women experienced a regular pattern of bleeding. Discontinuations for bleeding-related problems were less than half of those seen with progestogen-only injectables, and the discontinuation rates for amenorrhoea were low.

A common concern of women using hormonal methods is how quickly fertility is restored after stopping the method. Several studies suggest that ovulation is restored within a few months after the discontinuation of Cyclofem and Mesigyna, sooner than is the case with progestogen-only injectables. The experts noted these findings, but urged that more information be collected on the return of fertility now that large numbers of women can be followed in the introductory trials that are currently under way.

Metabolic studies are conducted to try and anticipate the effects of hormonal contraceptives on the risk of diseases such as cardiovascular disorders. In the case of Cyclofem and Mesigyna the preparations were found to have very little effect on blood coagulation and cholesterol. In fact, with regard to coagulation, Cyclofem and Mesigyna fared better than current combined oral contraceptives.

The experts concluded that Cyclofem and Mesigyna could be used by all potential contraceptive users. They may be particularly suitable for

In developing Cyclofem and Mesigyna women's needs and perceptions were kept at the forefront; a specific aim was to reduce the incidence of irregular bleeding seen with the progestogen-only injectable contraceptives.

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Cyclofem and Mesigyna are reversible once-a-month combined injectable preparations that are particularly suitable for women who wish to delay their first pregnancy and those seeking to space or limit births.

women who wish to delay their first pregnancy or those seeking to space or limit births.

However, as is the case with all hormonal contraceptives, Cyclofem and Mesigyna are not suitable for women with current breast cancer or genital tract malignancy or for women who are known or suspected to be pregnant. As with other combined progestogen–estrogen preparations, they should not be used by women who are breast-feeding.

Source: Facts about once-a-month injectable contraceptives: Memorandum from a WHO meeting. *Bulletin of the World Health Organization*, 1993, 71(6): 677–689. Reprints of this paper are available on request from the Programme.

New video

Choice not chance

This 20-minute video was produced on the occasion of the 20th Anniversary of the Programme. It highlights the global problems of rapid population growth and reproductive health and makes a case for continued research on reproductive health in general and fertility regulation in particular. The video provides an overview of the Programme's current objectives and strategies, emphasizing the importance of both biomedical and social science research.

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New Publications

The impact of infection on reproductive health

Edited by: A. Hinting, R. Bandaso, and P.J. Rowe
Published by Mediproc Publishing, Surabaya, 1993

Proceedings of an international symposium jointly organized by the Faculty of Medicine, Hasanuddin University, the National Family Planning Coordinating Board, and the World Health Organization.

Steroid hormones and uterine bleeding

Edited by: N.J. Alexander and C. d'Arcangues
Published by the American Association for the Advancement of Science, 1992

This book is the result of a meeting held at the US National Institutes of Health in 1992. By integrating basic biomedical research and clinical experiences, the book helps to clarify the mechanisms of endometrial bleeding, both in the normal menstrual cycle and when it is disturbed by exogenous hormones.

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