

Rationale, design, and cohort enrolment of a prospective observational study of the clinical performance of the new contraceptive implant (Femplant) in Pakistan

Syed Khurram Azmat¹
 Waqas Hameed¹
 Anja Lendvay²
 Babar Tasneem Shaikh³
 Ghulam Mustafa¹
 Muhammad Ahmed
 Siddiqui¹
 Sajid Brohi¹
 Asif Karim¹
 Muhammad Ishaque¹
 Wajahat Hussain¹
 Mohsina Bilgrami¹
 Paul J Feldblum²

¹Research, Monitoring and Evaluation Department, Marie Stopes Society, Karachi, Pakistan; ²FHI 360, Durham, NC, USA; ³Health Services Academy, Islamabad, Pakistan

Introduction: The use of hormonal implants has gained positive traction in family planning programs in recent times. Compared to other popular methods, such as long-term reversible intrauterine devices, the use of hormonal implants as a family planning method has distinct advantages in terms of long-term efficiency and better user compliance and availability. This paper presents a study protocol to document and evaluate the efficacy, safety, and acceptability of Femplant (contraceptive implant) in Pakistan during the first year of its use among married women of reproductive age (18–44 years) at clinics in two provinces of Pakistan (Sindh and Punjab).

Materials and methods: A total of 724 married women were enrolled in a noncomparative prospective observational study. The study involved six government clinics from the Population Welfare Department in Sindh Province and 13 clinics run by the Marie Stopes Society (a local nongovernmental organization) in both provinces. The participation of women was subject to voluntary acceptance and medical eligibility. All respondents were interviewed at baseline and subsequently at each scheduled visit during the study period. Side effects, complications and adverse events, if any, were recorded for every participant at each visit to the facility.

Discussion: Over the next 5-year period (2013–2018), 27 million hormonal implants will be made available in lower- to middle-income countries by international donors and agencies. The evidence generated from this study will identify factors affecting the acceptability and satisfaction of end users with Femplant (Sino-implant II). This will help to guide policies to enhance access to and the use of long-acting contraceptive implants in Pakistan and similar developing countries.

Keywords: safety, efficacy, acceptability, implant, Femplant, contraception, family planning, Pakistan

Introduction

Reversible long-term contraceptive methods (LTCMs), including intrauterine devices (IUDs) and implants, have a proven record of long-term effectiveness, convenience, and high user satisfaction.^{1,2} When compared with short-term methods, hormonal implants are more reliable, have better efficacy (>99%), are more cost-effective, and demonstrate high method-continuation rates (80% at 2 years postinsertion).^{3,4,5–9} Due to convenient use and better availability, implants are becoming increasingly popular when used in family planning programs.⁴

Hormonal implants are considered safe and suitable for nearly all women.¹⁰ They also offer great promise and privacy in helping to meet the needs of younger women,

Correspondence: Syed Khurram Azmat
 Research, Monitoring and Evaluation
 Department, Marie Stopes Society,
 21C Commercial Area,
 Old Sunset Boulevard, DHA-2, Karachi,
 Sindh 75300, Pakistan
 Tel +92 21 3538 9151
 Fax +92 21 3580 3262
 Email khurram.azmat@mariestopespk.org

who often face social and cultural barriers to accessing effective modern contraception.¹¹

The implants are made of thin, flexible, matchstick-sized rods of soft plastic.¹² The rods contain progestin hormone, and are surgically placed beneath the skin of a client's upper arm by a trained provider, who performs a minor surgical procedure under local anesthesia to insert or remove the rods. Implants can be removed whenever a woman wishes to have them removed, and thus they do not affect the return to fertility.⁶

Complications are uncommon, but may include infection (3%–7%) at insertion sites, difficulties in removal, and rarely expulsions. The use of hormonal implants is commonly followed by changes in bleeding patterns including lighter bleeding, fewer days of bleeding, irregular bleeding lasting more than 8 days, infrequent bleeding, and no monthly bleeding. About 20%–30% of clients may experience few other minor side effects, such as headache, abdominal pain, acne, changes in weight, breast tenderness, dizziness, changes in mood, and nausea. However, these changes eventually diminish with time.^{13,14} Although the acceptability of bleeding disturbances varies in different cultures, studies have pointed out that efficacy and safety, factors related to simplicity, ease of use, acceptability, satisfaction, and contraceptive benefits can play a role in influencing the adoption of hormonal methods and determining consistency of use.^{5,15,16}

Context

Of the 208 million unintended pregnancies in 2008, nearly 90% occurred in the developing world.¹⁷ In 2012 alone, more than 220 million women in the developing world had an unmet need for modern contraception, although this number had decreased from 226 million in 2008.¹⁸ However, the unmet need for modern contraception in 69 of the world's poorest countries has seen an increase of 9 million (from 153 to 162 million women) between 2008 and 2012, and thus accounts for 73% of all unmet need in the developing world.¹⁸

This high unmet need for contraception, as well as contraceptive failures in the developing world, was responsible for 80 million unintended pregnancies in 2012. Out of those, 40 million ended in abortions, 30 million in unplanned births, and the remaining 10 million were terminated as miscarriages.¹⁸ Access to contraception is low among women who are poor, less educated, rural, and young (aged 15–24 years).^{18,19} Almost 99% of maternal deaths occur in low-resource countries.²⁰ The risk of maternal morbidity and mortality is higher among poorer women, who have less

access to modern contraception, including implants.²¹ Among the women whose needs for contraception are met, many use less effective and supply-dependent methods. These include short-acting methods that require users continually to stock up their contraceptive supplies, as they do not have access to highly effective and more convenient long-term methods, such as implants.¹¹

It is estimated that meeting the unmet need for contraception could reduce maternal mortality by 29% and prevent more than 100,000 maternal deaths each year globally.²² Additionally, satisfying the unmet need for modern contraception in developing countries would further prevent 54 million unintended pregnancies, including 21 million unplanned births, 26 million abortions (of which 16 million would be unsafe), and 7 million miscarriages; this would also help to prevent 1.1 million infant deaths.¹⁸

Globally, 56% of married women aged between 15 and 49 years use a modern method of contraception. However, the worldwide implant-prevalence rate is extremely low, at 0.3%. Interestingly, very few countries – including some of the very developed or developing countries – document the highest implant-use rate in the world, which ranges from 1% to 6%.⁷ The reasons cited for the low use of implants, particularly in developing countries, include:

- for clients, the initial high cost of implants compared with other contraceptive methods;
- for service providers, lack of formal training on insertion and removal of implant.

The use of implants as an LTCM can be considered cost-effective provided the discontinuation rate remains low, one of the reasons for which is lack of formal training on insertion and removal.⁵ However, studies have shown that a huge number of women would choose implants or other long-term methods if these were available.¹⁶

Complications during pregnancy and childbirth remain the most frequent cause of death for women in Pakistan, as in other developing countries.²³ Each year, around 12,000 maternal deaths occur in Pakistan due to pregnancy-related complications.^{24,25} The risk of a woman dying as a result of pregnancy or childbirth during her lifetime is about one in 4,700 in developed countries.²⁶ In Pakistan, on the other hand, the risk is about one in 89.²³ The high fertility rate of 4.1 children per woman is highest among women who are poor, uneducated, and live in rural areas. Of every four pregnancies, one is unplanned. Modern contraceptive use has remained stagnant at around 30% for over a decade. At 25%, the unmet need for contraception remains unacceptably high, especially for women in the lowest income quintile (at 31%), women

with less education, and women in rural communities. Use of modern contraceptive methods among currently married women stands at 22%, and is further lower among women in rural areas – 17%. Short-term and permanent methods are the most common contraceptive methods used in Pakistan, while the use of long-acting and reversible methods like IUDs and implants is only 2.3% and 0.1%, respectively.²³ If only 4% of current oral contraceptive users (100,000 women) in Pakistan switched to IUDs or implants, it is estimated that more than 25,000 unintended pregnancies could be averted over a 5-year period.²⁷

Some studies from developing countries have suggested that poor screening, insufficient counseling, and health concerns could be some of the reasons for the lower use of LTCMs.^{28,29} However, these studies mainly looked at determinants of contraceptive uptake, rather than reasons for continuation or discontinuation. Therefore, a lack of empirical evidence on LTCMs has been identified as one of the most important gaps in promoting and increasing their use in Pakistan.²⁹

The contraceptive method: Femplant

The two-rod subdermal contraceptive implant Sino-implant (II) (Shanghai Dahua Pharmaceuticals, Shanghai, People's Republic of China) is one of the most effective contraceptives available today.⁸ It was registered as Femplant in Pakistan in 2010. Like Jadelle® (Bayer, Leverkusen, Germany), another implant system, the Chinese product contains 150 mg of levonorgestrel in two rods, and it has an annual pregnancy risk of lower than 1%. However, the per-unit wholesale cost of Femplant (approximately US\$8) in the year 2010–2011 was considerably lower than the current public sector price of Jadelle (\$21), but in early 2013 Jadelle's public sector price dropped to \$8.50.³¹

Femplant is a set of two flexible, cylindrical rods made of milky-white, medical-grade silicone elastomer. Each rod contains 75 mg of levonorgestrel, the active ingredient. The rods are inserted into tubes composed of a colorless, transparent form of silicone elastomer. Both ends of each tube are sealed with an adhesive. Levonorgestrel, a progestin, is a synthetic hormone. It mimics progesterone, a potent inhibitor of sex hormones secreted by the pituitary gland. Like progesterone, levonorgestrel suppresses ovulation. It also thickens cervical mucus, which impedes the migration of sperm. Femplant is indicated for women of childbearing age who wish to use an LTCM.

The two Femplant contraceptive rods are usually inserted during the first week of a woman's menstrual cycle (starting

from the first day of menstruation), or at any other time when it is reasonably certain that the woman is not pregnant. A 0.2 cm-long incision is made in the skin of the upper arm or in the inside of the thigh, and the rods are implanted beneath the skin with a trocar (surgical instrument) under local anesthesia and aseptic conditions. An adhesive bandage is applied to cover the surface of the incision, and then the limb is wrapped with gauze.

Femplant provides effective contraception for at least 4 years. Medical contraindications include current (history of) breast cancer; severe liver disease; acute deep venous thrombosis or pulmonary embolism; unexplained vaginal bleeding; lactation during the first 6 weeks postpartum; and systemic lupus erythematosus with positive or unknown antiphospholipid antibodies.¹⁰

The adverse effects of Femplant are similar to other levonorgestrel-releasing implants (eg, Jadelle, Norplant). The vast majority of levonorgestrel-implant users experience menstrual problems, but serious bleeding problems are not more frequent than in controls. Other adverse events (AEs) may include skin conditions, headaches, dizziness, nervousness, weight change, anxiety, and nonclinical depression. Most of these side effects are mild, and normally resolve spontaneously after several months of use. More serious AEs (ie, hypertension, gallbladder disease) are rare.²⁹

For over 50 years, progesterone has been used in the treatment of recurrent endometrial cancer in the form of pills, injections, implants, and long-acting progestin IUDs, which are also known as the levonorgestrel intrauterine system (LNG-IUS). This LNG-IUS is used especially in breast cancer patients taking tamoxifen (TAM) to prevent endometrial proliferation. A recent systematic review, though, concluded that there was no significant relationship between breast cancer and the use of long-acting progestin-releasing devices, such as LNG-IUS, but still unclear about the possible effects of Mirena® (Bayer) or LNG-IUS on the breast. Therefore, the use of any long-acting progestin-only device, whether for an IUS/IUD or implant, requires both caution and more detailed clinical evidence for decision making, which right now is limited.³⁰

Rationale for the study

The contraceptive effectiveness and safety of Sino-implant (II) was evaluated in 15 clinical trials, all conducted in the People's Republic of China.¹⁴ Outside these clinical trial settings, more than 7 million units of Sino-implant (II) have been distributed, mainly in the People's Republic of China and Indonesia. Although the documented clinical experience

with Sino-implant (II) outside these Asian countries is limited, preliminary data (during the first of year of use) from a study conducted in Madagascar in 2012 documented promising levels of safety, effectiveness, and acceptability of Sino-implant (II).³¹ Therefore, the findings of this study will contribute to the body of knowledge on the clinical performance of Femplant outside the People's Republic of China, Indonesia, and Madagascar.

Study partners

The Marie Stopes Society (MSS) is one of the leading nongovernmental organizations in Pakistan, and has been providing a full range of high-quality family planning and reproductive health services to save and improve women's lives. The MSS is part of the Marie Stopes International (MSI) global partnership, committed to and recognized for the highest clinical and operational standards. FHI 360, with support from the Bill and Melinda Gates Foundation, provided technical assistance to facilitate the introduction of Sino-implant (II) (registered by the MSS in Pakistan as Femplant) – a low-cost, highly effective contraceptive implant – in resource-constrained countries. With funding from the US Agency for International Development, FHI 360 entered into a partnership with the MSS, and provided financial and technical assistance to implement the prospective cohort study with the aim of assessing Femplant safety, effectiveness, and acceptability in Pakistan. Engender Health has also implemented a prospective cohort study in Bangladesh.

Study objective

This study aimed to evaluate the contraceptive effectiveness, safety, and acceptability of Femplant during the first year of its use in Pakistan. Specific objectives were to conduct the postapproval monitoring of:

- the contraceptive effectiveness of Femplant during the first year of use
- safety of Femplant during the first year of use
- side effects and complications during Femplant insertion or removal
- acceptability of Femplant during the first year of use
- women's satisfaction with Femplant services.

Study design

This was a noncomparative prospective observational study of women using Femplant as a primary method of contraception in the two most populous provinces of Pakistan – Sindh and Punjab. The provinces were selected on the basis of high levels of population concentration, similar sociodemographic characteristics, and relatively better law-and-order situa-

tions compared with other provinces. Overall, the study was conducted in a total of 19 clinics, including six government clinics from the Population Welfare Department (PWD) in Sindh, and 13 clinics run by the MSS nongovernmental organization in both provinces. These clinics had sufficient expected client flow per month and were geographically (urban- or periurban-based) accessible, facilitating enrollment and follow-up of women in the prospective study.

A total of 724 women, divided into two cohorts, were enrolled in this 1-year prospective study, comprising:

- a prospective cohort consisting of 392 women who were followed up at 3 and 12 months after enrolment
- a surveillance cohort of 332 women who returned to the clinic within 12 months after enrollment if they experienced complications, medical problems, pregnancy, or wanted to remove the Femplant.

Originally 600 women were supposed to be enrolled but during the course of study enrollment, there were 124 overenrollments. This overenrollment was communicated to the Pakistani and FHI 360 institutional review boards (IRBs).

Prior to initiation of the study, we randomly designated clinics to enroll women into either the prospective or surveillance cohorts. Women were recruited into the study during their routine family planning visit at either the participating government-run or MSS clinic. During the initial visit after the woman had selected to use the Femplant as her contraceptive method, research staff introduced and explained the study objectives and procedures and potential risks and benefits of participation. Women who agreed to participate in the study were asked to sign a consent form documenting their voluntary decision to join the study. After signing the informed consent form, each potential participant was evaluated for medical eligibility and admitted into the prospective or surveillance cohort, depending on which arm the clinic had been allocated to. Women in the prospective cohort were asked to return to the clinic both 3 and 12 months after the Femplant insertion to be interviewed and evaluated for pregnancy, AEs, and method acceptability. Women in both cohorts were encouraged to return to the clinic at any time if they experienced medical problems or other problems related to the implant, or became (or suspected that they might be) pregnant, or if they wanted to remove the implant.

Study population and inclusion criteria

Married women of reproductive age (MWRA) were qualified to participate in the study. To be eligible for inclusion,

women had to be between 18 and 44 years of age, inclusive. They must have chosen to use Femplant for contraception, be medically eligible for this method of contraception, and give informed consent.

Sample size/sampling strategy

The sample estimation was based on the following assumption: if we enroll 300 women and assume that loss to follow-up at 12 months is less than 20% and the true 12-month cumulative probability of pregnancy is no more than 1%, then we will have a 90% chance of both ruling out a 4.5% pregnancy probability (ie, obtaining an upper 95% confidence bound of less than 4.5%) and obtaining an estimated 1-year pregnancy probability of less than 2%. Our assumptions of the first-year probability of pregnancy were based on data from the four randomized trials with a total of 15,943 women assigned to Sino-implant (II) that showed first-year probabilities of pregnancy ranging from 0.0% to 0.1%.⁸

Timeline

The overall duration of this study was about 26 months: from October 2010 to January 2013. The first 5 months comprised writing the study protocol, developing study instruments and securing ethical approval from the IRBs from FHI 360 and Pakistan. The field component consisted of recruitment, and follow-up took about 16 months. Data entry, analyses, and report writing were carried out in the final 4 months.

Study setup, visits, and procedures

Admission

Once enrolled in the study and after the implant was inserted (as described earlier), all women underwent the baseline interview. After the baseline interview, all MWRA in the prospective cohort were asked to return to the clinic both 3 months and 12 months after the insertion to be interviewed for complications, AEs, and acceptability, and to be evaluated for pregnancy. Women in both cohorts were asked to contact or return to the clinic if they experienced any medical problems or pregnancy while using the implant, or if they wanted to remove the implant.

Visits at 3rd and 12th month

During each follow-up visit, a research nurse conducted the follow-up interview and completed the appropriate case-report form (CRF). A pregnancy test was administered at the month 3 visit, only if clinically indicated (eg, absence of

menses for more than 6 weeks, other signs and symptoms of pregnancy, or woman's concern that she may be pregnant), and in all women at the month 12 visit. Pregnant women were provided with counseling regarding their pregnancy options, implant removal, and prenatal care. If the woman wanted to or already had removed the Femplant, she was provided with family planning counseling as part of the standard of care. All efforts were made to contact women in person through phone calls on the numbers provided by them or approaching them through persons who had referred them to the study clinics.

Unscheduled visits

During unscheduled visits, regular follow-up procedures were followed and study CRFs completed, if appropriate. Where personal contact was not possible, the follow-up interview was conducted via phone. All women were encouraged to seek medical care in the clinics where the implant was inserted or elsewhere if they experienced any medical problems or suspected that they may be pregnant after the study was over.

Retention

Measures to improve retention

The study staff emphasized to each participant the importance of follow-up for the entire study period and the need to return for the follow-up visits. As mentioned earlier, participants were compensated for their transportation costs and time to attend the scheduled visits for an amount approved by the participating IRBs. Clinic staff collected contact information for each participant. If a participant missed a scheduled appointment, the clinic staff tried to locate her using all possible means (eg, telephone, mail contact, through referees, or possibly in person) and documented these attempts (at least three attempts were made). The study staff also collected contact information from each participant for a contact person who would know where the participant might be. With participants' consent, these people were to be contacted in case the participant could not otherwise be found.

Study outcomes were:

- with the Femplant in place, the cumulative probability of pregnancy through 1 year
- prevalence and incidence rates of immediate and delayed complications associated with insertion or removal of the Femplant
- incidence rate of AEs related to use of the Femplant

- cumulative probability of early discontinuation of the Femplant through 1 year
- reasons for discontinuation of Femplant
- level of women's satisfaction with Femplant services.

Measurement of study outcomes

For 392 women enrolled in the prospective cohort, data related to satisfaction with MSS services, pregnancy, AEs, insertion complications, and acceptability information were collected through interviews and review of medical records during admission, follow-up at months 3 and 12, and during unscheduled visits. This information was documented on the corresponding CRFs. In addition, for another 332 women enrolled in the surveillance cohort, data related to the main study outcomes were collected through an interview during unscheduled visits and documented on the corresponding CRFs.

Measurement of pregnancies

A rapid urine pregnancy test (available through the MSS in Pakistan) was performed during the month 3 or unscheduled visits, only if clinically indicated. At the month 12 visit, a pregnancy test was performed in all 392 participants from the prospective cohort. The study staff ensured that information about all study pregnancies was documented on the follow-up and pregnancy-outcome forms accordingly. Whenever possible, date of conception was estimated based on the available information (date of last menses, etc). Pregnancies diagnosed elsewhere (ie, without confirmation in the study clinic) were considered study pregnancies.

Measurement of insertion/removal complications

The study staff reviewed the existing medical records for immediate insertion complications during the admission visit and documented it on the baseline form. All information related to delayed complications of the insertion procedure was collected during the month 3 or unscheduled visits, and documented on the follow-up form and serious AE (SAE) form, if appropriate. All complications related to removal (if occurring during the study) were documented on the follow-up and SAE forms, if appropriate.

Measurement of adverse experiences

Research staff collected information on all SAEs and bleeding problems that women reported during the month 3, month 12, or unscheduled visits (see the Safety section for

more details on collecting safety data). The staff ensured that all safety information was documented on the follow-up and SAE forms, if appropriate.

Measurement of acceptability and continuation

Acceptability was evaluated based on continuation rates and reasons for discontinuation. It was also measured by responses to the acceptability questions during the follow-up interviews at the month 3, month 12, or unscheduled visits. In addition, information on acceptability and continuation was extracted from the existing records. The research staff made sure that all relevant acceptability information was documented on the follow-up form.

Measurement of women's satisfaction with Femplant services

Information concerning women's satisfaction with Femplant services was measured by responses provided during baseline interviews and during the admission visit, and documented on the baseline form.

Completion of the study

A participant was considered to have completed the study:

- in the prospective cohort – after she had completed her month 12 follow-up visit, and after her final set of data had been collected and entered on the appropriate study CRFs
- in the surveillance cohort – after the 12-month follow-up of the prospective cohort had been completed and all data had been entered on the study CRFs
- in both cohorts – after she had become pregnant while using Femplant.

Loss to follow-up

If a participant in the prospective cohort did not have any indication that the implant was removed and failed to appear for the scheduled 3- and/or 12-month visit, she was presumed lost to follow-up. Study files of participating MWRA who missed their appointments were kept open until study close in case they returned later for follow-up. If the participant did not return to the clinic before the study closed, the follow-up form (namely, the final status question) was completed at the time of study close. The form would indicate that the participant was lost to follow-up; this designation was not made for any participant until the closing date of the study. "Lost to

follow-up” was not applicable to participants in the surveillance cohort.

Study discontinuation

Participants were informed that they could withdraw from the study at any time, for any reason, without loss of other benefits or services to which they were entitled. We would discontinue participants from the study if any of the following occurred:

- investigator or other physician decided that continued participation in the study would be harmful
- study was terminated, and/or other administrative reasons
- participant decided to or had already removed the implant
- participant decided to withdraw her participation in the study.

The study staff documented the reasons for early discontinuation of the Femplant on the follow-up form. Even when early discontinuation from the study occurred, the staff made reasonable efforts to collect and assess information relevant to the study outcomes at the time of discontinuation. We did not replace any discontinued or lost-to-follow-up participants.

Safety

Scope of safety data

An AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study product, whether or not this was considered to be related to the product. Preexisting conditions were not considered AEs unless they increased in frequency or severity or changed in nature.

In this study, during both scheduled and unscheduled visits, we collected information on the following:

- SAEs
- immediate and delayed insertion complications
- immediate and delayed removal complications
- vaginal bleeding problems.

Operational definitions

An SAE was defined as any experience that suggested a significant hazard, contraindication, side effect, or precaution. An SAE included any adverse experience resulting in any of the following outcomes:

- death
- a life-threatening adverse drug experience

- inpatient hospitalization (including overnight stay) or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth.

All reported SAEs (other than insertion complications) were graded for severity as follows:

- mild (participant was aware of the AE all of the time, but was still able to do all activities)
- moderate (participant had to discontinue some activities due to the AE)
- severe (participant was incapacitated by the AE and unable to perform normal activities).

All reported SAEs were graded for relatedness to the Femplant as follows:

- unrelated (onset of the AE had no reasonable temporal relationship to administration of the study product, or causal relationship to administration of the study product was biologically implausible, or the event was attributed to an alternative etiology)
- possibly related (onset of the AE had a reasonable temporal relationship to study-product administration, and a causal relationship was not biologically implausible)
- definitely related (onset of the AE showed a distinct temporal relationship to administration of the study product, or the AE was a known reaction to the product or chemical group or could be predicted by the product’s pharmacology).

All immediate and delayed insertion and removal complications were graded for severity as follows:

- mild (did not require any medical intervention)
- moderate (only required resting or minimum level of medical intervention, such as taking pain medication)
- severe (required attention from medical personnel to conduct a medical intervention).

Documentation and reporting of safety data

All SAEs in this study were documented on the follow-up and SAE forms and reported to FHI 360 using the SAE report form within 24 hours of the study site becoming aware of the problem, and if required to the local regulatory authorities and IRB, according to their policies. FHI 360 would report all SAEs in this study to FHI 360’s Protection of Human Participants Committee (PHSC), according to FHI 360’s standard operating procedures.

All insertion and removal complications, as well as bleeding problems, were documented on the follow-up form. If any of these medical problems met the definition of an SAE, the

SAE form would have to be completed. For all SAEs related to bleeding problems or removal that occurred during the study, the standard SAE-reporting requirements were followed. Since the insertion was not part of this prospective study, SAEs related to the insertion would not be reported to FHI 360, but might be reported by the MSS to the regulatory authorities or local pharmacovigilance program in Pakistan as appropriate.

Pregnancy was a study outcome, and was not documented as an adverse experience. Information related to all study pregnancies was documented on the follow-up and pregnancy-outcome forms.

Social harm events

A social harm event was defined as an adverse social consequence or outcome due to study participation. If the site principal investigator (PI) learned of a social harm event, he/she would report the event on the social harm event form to FHI 360 and the IRB within 3 days of becoming aware of the event.

Data management

A detailed data-management plan was outlined prior to initiation of the prospective study. The following is a brief summary of the plan. Study research assistants captured data obtained during the follow-up interview or transcribed the data extracted from the existing medical records on a two-ply paper CRF. The original copy was kept in the participant's original file folder at the site for monitoring purposes, and the other copy was sent to the MSS local office for double data entry using EpiData version 3.1 (EpiData Association, Odense, Denmark).

The electronic datasets were available for interim and final review and analysis to the research staff at MSI and FHI 360. Details of data ownership and sharing between MSI and FHI 360 were specified in the final version of the data-management plan.

Monitoring plan

A study coordinator worked with the study nurse at each site and regularly monitored whether the study protocol, data-collection process, and questionnaires were being properly followed. The following were monitored:

- any changes in the protocol that had been reported to the head of the Research, Monitoring and Evaluation Department at the MSS and subsequently to the MSI project manager
- whether participants' records were complete and accurate

- a log with participants' names, addresses, clinic file numbers, and study participant numbers in a confidential location
- whether the study service-inventory log was current and showed the total number of procedures carried out
- whether any SAEs were being promptly documented and reported
- whether physicians and other study staff were carrying out their activities as agreed upon prior to study initiation.

Analysis plan

A draft analysis plan was developed by FHI 360 and MSI prior to the initiation of the study. The following is a summary of the planned analysis. For the 392 women enrolled in the prospective cohort of this study, all information related to the study outcomes obtained through the follow-up interview was documented on the study CRFs. In addition, all information related to the main study outcomes for the other 332 women enrolled in the surveillance cohort was extracted from existing medical records or obtained during unscheduled contacts and visits, documented in the study CRFs, and included in the final analysis.

Descriptive statistics were used to analyze demographic and baseline characteristics. We used measures of central tendency and dispersion for continuous variables, including means, medians, standard deviation, and range. Categorical data were summarized with frequencies and percentages.

All SAEs reported during the study were supposed to be summarized in frequency tables (including both the number of each type of SAE and the number of distinct participants with each type of SAE); however, none had been reported at the completion of the study. Prevalence and incidence rates were calculated for immediate or delayed complications associated with insertion and/or removal. Rates of early discontinuations of the Femplant were computed, and reasons for discontinuation were summarized and presented in a tabular format. The 1-year cumulative probability of pregnancy and corresponding 95% confidence interval were computed using life-table methods, recording women at the time of implant removal or at the time of their last clinic visit, whichever came first. Women with no clinical indication of pregnancy (and hence no pregnancy test) were considered not to be pregnant through the time of their last clinic visit. Bleeding problems and rates were computed and presented in a tabular format.

Potential risks and benefits

Potential benefits to participants

This study had no expected direct benefits to participants. However, the findings from this study should generate additional knowledge on the clinical performance of the Femplant and will benefit potential users of this method in the future. Participation in the study did not affect fees, payment, billing, or reimbursement for any other services at the clinic. Participants were, however, compensated for their time and trouble in completing the month 3 and month 12 visits in the amount of Rs250 per participant per visit (equivalent of ~US\$2.30).

Potential risks to participants

All possible efforts were made to prevent loss of confidentiality during the study. Participation in this study had no other expected risks to participants. All women participating in this study had personally and voluntarily chosen to use the Femplant for contraception before they were invited to participate in this prospective study. Study participants might have experienced certain side effects, including minimal risk of pregnancy, but these risks might have been due to use of the Femplant and not due to their participation in this study.

We had not anticipated any social harm events for participants during the study, and no social harm event was reported during the course of the study. Despite that, we carefully monitored and intended to act accordingly if there was any unacceptable risk of social harm events resulting from participation in the study.

Ethical considerations

Institutional review boards

All investigators and research staff involved in the study had a commitment to respecting the ethical principles of clinical research. The study protocol, the informed consent form, and other appropriate documentation were reviewed and approved as required by the PHSC at FHI 360 (FWA00016827).

The study also received full clearance from the Ethics Review Committee of the National Bioethics Committee of the government of Pakistan, reference number 4-8711/NBC/-65/RDC/386. The study is also archived at <http://apps.who.int/trialsearch/trial.aspx?trialid=NCT01463254>.

Participating research staff were also trained in research ethics. The PI at the research site was responsible for ensuring that all requirements of the local IRB were met. Before implementing any changes to the protocol, informed

consent, advertising, or written materials for participants, the site PI made sure that all of the changes were approved by FHI 360's PHSC and the local IRB, except where necessary to eliminate immediate hazards to human participants. The PI was also responsible for notifying FHI 360 and MSI as soon as possible, after no more than 48 hours, if the local IRB withdrew its approval of this research at any time before its completion.

The site PI was also responsible for making progress reports to the local IRB and to FHI 360 and MSI annually and within 3 months of study termination or completion. These reports could include the total number of participants enrolled, the numbers and reason(s) for discontinuation, a description of all SAEs, the number of participants completing the study, all changes in the research activity, and all unanticipated problems involving risks to human participants or others. Copies of all study-related correspondence with the local IRB were also sent to FHI 360 and MSI.

Informed consent

The study staff explained the study and its associated procedures, risks, and benefits to the participants. The consent form was read verbatim to each participant. Each eligible participant was asked to sign the informed consent form if she wished to participate in the study. The consent form was written to be understandable for a 14-year-old (grade 8 reading level). The informed consent document was translated from English into the local Urdu language. It was made sure that each participant agreed to and understood the risks and benefits associated with her participation in this study, her rights to terminate participation in the study without affecting her health care at the site, whom to contact with questions regarding the study, and that she had freely given informed consent to participate in the study and to have her existing medical records related to the use of the Femplant reviewed and analyzed as part of the study. A friend/relative accompanying the woman or a clinic staff member not involved in implementing the study signed the informed consent form to confirm witnessing the agreement to participate in the study for all illiterate participants.

Due to the long-term nature of the implant and possible extension of the follow-up period of the study, all women were informed of the possibility of more annual follow-up contacts and asked for their permission to be contacted in the future. A copy of the signed informed consent form was also given to the consenting women. Therefore, the signed informed consent form became a permanent part of the

participant's study records. It was stored separately from other participants' records related to the study to protect their confidentiality.

Participants' confidentiality

Except as required by law, all study staff were committed to protecting the confidentiality of participants to the fullest extent in order to protect their rights and welfare. Participants' contact information and informed consent documents with names were stored separately from the study CRFs. No participant's personal identifiers appeared on any data or documentation sent to MSI or FHI 360. Participants were not identified by name in any report or publication resulting from the study data. Risk of loss of confidentiality might have occurred if these procedures were inadvertently breached. All possible efforts were made to prevent this from happening. The PI at the site permitted trial-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data and other study-related documentation.

Report writing and dissemination plan

The FHI 360 and MSI research teams, working in close collaboration, will determine a detailed data-analysis strategy and final report outlines, and describe it in the data-management and analysis plans prior to conclusion of the data collection. FHI 360 will perform analyses as specified in the analysis plan and draft a final report based on the data. A publication is planned following completion of the study.

Discussion

The research evidence from this study will help to identify factors affecting the acceptability of and users' satisfaction with the Femplant (ie, Sino-implant [II]), and help to enhance access to and use of long-acting contraceptive implants in Pakistan and similar developing countries. The need for such research evidence has become more pertinent since international donors, including Bayer and the World Health Organization, joined forces to make 27 million implants available in resource-constrained countries from 2013 to 2018.³² Further, there is a dearth of evidence available on the effectiveness and safety of this method outside the People's Republic of China and Indonesia. Therefore, more specifically, the findings of this study will contribute to the body of knowledge on clinical performance in Pakistan, which will provide timely recommendations for the successful introduction/marketing of this new LTCM in the country. Further, this new implant will fill the gap of need for a reliable and quality LTCM in

the wake of PDHS findings of a fertility rate of 4.1 children per woman and only 0.1% of current implant use.²³

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Disclosure

The authors report no conflicts of interest in this work.

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