### Bibliographic Input Sheet

**Primary Subject Classification**: Family planning

**Title and Subtitle**: Assessment of IUD performance

**Authors**: Kessel, Elton; Thomas, K.N.; Wheeler, R.G.; Bernard, R.P.

**Document Date**: 1976

**Number of Pages**: 20

**Reference Organization**: IFRP

**Supplementary Notes**: (Sponsoring Organization, Publishers, Availability)

**Abstract**:

**Control Number**: PN-AAF-384

**Descriptors**: Assessments, Contraceptives, Family planning, Intrauterine device

**Project Number**: CSD-2979 Res.

**Type of Document**: AID 590-1 (4-74)
ASSESSMENT OF IUD PERFORMANCE

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This work was supported in part by the International
Fertility Research Program, Research Triangle Park,
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Abstract

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Standard measures used to assess events occurring in IUD use are described. Many illustrations are given of life table rates of the pertinent events of pregnancy, expulsion, and removal for pain or bleeding. The effect of surface area, width, and size of IUDs on these event rates is shown. The influence of characteristics of the IUD wearer including age, parity, previous abortions, race, ethnic background on IUD performance is depicted from results of field trials. The skill and experience of the person inserting the IUD and providing follow-up care is also shown to influence all three pertinent event rates. A more sensitive approach to evaluation of bleeding than removals is suggested and the usefulness of ranking of event rates of several IUDs is shown.

It is concluded that carefully conducted clinical trials with random assignment of devices to subjects is essential to control for influences of both the physician and the IUD wearer in comparing two or more IUDs.

A strategy for IUD performance assessment is described, including preclinical examination of IUDs, early clinical trials, the definitive clinical trial and post-marketing surveillance of IUD use.

Finally, the role of the field trial organization in facilitating the assessment of new IUDs is described.
INTRODUCTION

A large body of knowledge now exists on the performance of intrauterine contraceptive devices (IUDs). Cooperative studies have been conducted by The Population Council, The Pathfinder Fund, Exeter University and the International Fertility Research Program. The common language imposed by these cooperative efforts has made possible comparisons between data sets around the world. Much of this data has been summarized in the proceedings of conferences (Tietze and Lewit, 1963; Segal, Southam and Shafer, 1965; Wheeler, Duncan, and Spiedel, 1974; Hefnawi and Segal, 1976) and in review articles (Tatum, 1972; Orleans, 1973; Huber, et al., 1975; Mishell, 1975).

The early work of Pearl (1933) did not differentiate long and short periods of IUD use for women under study. Vie1i (1967) suggested the application of life table methodology to account for this factor in measuring contraceptive use; this methodology has been well developed by Potter (1969) and by Tietze. Some differences in definitions still remain. Sivin (1976) has made suggestions for rationalizing these differences.

Rates for the pertinent events of pregnancy, first expulsion and removal for pain or bleeding have been the primary performance criteria used to assess new IUD designs. Gross rates of these events allow for the competitive risk among different events and are preferred when studying individual events. Net rates, however, are additive and are particularly useful for the assessment of total continuation rates, including reinsertions after expulsion. The use of net rates is preferred for the assessment of IUD performance in family planning programs.
While life table rates of the pertinent events of pregnancy, expulsion and removal are the measurements of choice in clinical trials of two or more IUDs, measurement in ordinal time from insertion may be inadequate for the evaluation of contraceptive programs or epidemiological investigations where events over calendar time and geographic locations are of paramount importance. Life table rates are not appropriate for events related to insertion, such as perforation with extrauterine placement of the IUD. Postmarketing surveillance of rare events related to IUD use requires additional criteria of measurement related to the relative risk of events in users and non-users of different IUDs.

FACTORS AFFECTING IUD PERFORMANCE

Numerous factors affect IUD performance. These include: 1) chemical and physical composition and geometrical configuration of the IUD, 2) skill of the inserter, 3) judgement of the professional providing follow-up care regarding need for removal, 4) tolerance of the recipient to side-effects, and 5) characteristics of the IUD recipient. Pregnancy and expulsion are dependent on the design and composition of the IUD and physiological status of the woman and, to a lesser extent, on the skill of the inserter. Removals for bleeding and pain, on the other hand, seem more dependent on the tolerance of both the IUD wearer and the judgement of her physician than the design of the particular IUD. Several illustrations will depict the influence of these factors.

Figure 1 shows the association of surface area of an IUD to be directly related to removals for bleeding or pain and inversely related to pregnancy failures.
Figure 2 shows the experimental M-device; two widths of this device—the M-213 with the narrow stainless steel band (2.36 mm) and the M-211 with the wide band (2.62 mm)—are compared in Figure 3. The differential pregnancy rate, with the wider M-211 is significantly lower than with the M-213. This figure also shows the remarkably low expulsion rate for either model of this device, the lowest rate for any IUD tested to date. Removals for bleeding and pain are comparable to those of the Lippes Loop.

That size of an IUD can affect its rate of expulsion is shown in Figure 4. Lippes Loops B and C, tested in Bombay, and C and D, tested in Baguio City, show that expulsion rates are lower for larger sizes. The figure also shows lower expulsion rates for postabortion than for postmenses insertions of the Lippes Loop C in Rijeka. The low event rates for the Lippes Loop D in Kainantu were attributed to the high age and parity of this group of women. Both age and parity are inversely associated with expulsion but age is probably more important than parity as seen in Figure 5.

In Figure 6, Bernard (1970) shows an interesting V-shaped effect on expulsion rate by number of previous abortions for low parity women. However, for high parity women, expulsion rates increase by any number of previous abortions. Apparently, after products of conception have been passed through a dilated cervix more than five or six times, the expulsion rate rises with additional abortions or deliveries.

The physiological effect of race on expulsion is seen in Figure 7. The expulsion rate for the Lippes Loop C was twice as high for African Blacks as for non-Blacks; the expulsion rate for the Loop D was also significantly higher among Blacks.
That expulsion may be related to the skill of the inserter is seen in the dramatic differences in expulsion rates for two studies of the T Cu-200 in Bangkok (Figure 8). Incomplete insertion to the uterine fundus is the likely explanation for the unusually high expulsion rate in one center. Similar differences have been reported for pregnancies between centers for this device in other studies (Jain, 1976).

Since lactating women are subfecund and it is well known that the rate of IUD expulsions is very high when insertions are performed immediately postpartum (Zatuchni, 1970), many physicians do not advocate immediate postpartum IUD insertion. However, in many societies it is difficult to provide contraceptive services except during hospitalization for maternity care. Potter (1971) has analyzed the risks of pregnancy related to expulsion and to delayed insertion and confirms the value of postpartum insertions.

Removals for bleeding or pain are both the most frequent and most variable events. Their effect on discontinuation rates in 50 studies is summarized by Bernard (1970) in Figure 9.

Women of lower age and parity are more likely to request removals for bleeding or pain as seen in Table 1.

That bleeding and pain removals can be dramatically different between centers is seen in Figure 10. Removals between the 6th and 24th ordinal month after insertion were 3.4, per 100 women in the Philippines compared to 18.9 in India.
The effect of the ethnic background of women on removals is seen in Figure 11. The removal rates for Orthodox Jewish women were 5 times the rates for other women at the same clinic in Israel, although the expulsion rates for the two groups were similar.

That removal for bleeding and pain may be related to the physician's experience is seen in Figure 12 which analyzes an early and later cohort of insertions by the same physician. Early in the study while she was relatively inexperienced, she removed 9.0 percent of the IUDs for bleeding and pain in the first postinsertion month compared to 2.5 percent later in the study.

A clear separation of pain and bleeding was seen in use of the Intrauterine Membrane (IUM) shown in Figure 13. In multiclinic trials, women reported few episodes of pain or uterine cramps (Wheeler, Laufe and Thomas, 1975). However, removals for bleeding were high, as was predicted from computer models used in its design (Wheeler, Buschbom, and Marshall, 1974).

The variables affecting bleeding removals have emphasized the need for quantitative blood loss studies for the assessment of new IUD designs; such studies are now being conducted by Hefnawi, et al. (1974) and by Morehead, et al. (1976). Another approach has been to find a more sensitive indicator event than removal for bleeding. Thomas has suggested using abnormal bleeding as reported by the women (Kessel, Bernard, and Thomas, 1976). Table II shows his application of this approach in a comparative study of plain and progesterone-releasing Spring Coil IUDs. Rodriguez, Faundes-Latham, and Atkinson (1976) have suggested pattern indicators such as the mean length of bleeding episodes and the mean length of each bleeding-free interval to describe the bleeding calendar of each acceptor. The pattern indicators of two or more IUD groups are
then compared to determine differences in bleeding experiences.

In summary, it appears that the chemical, physical and geometric makeup of an IUD can affect any of the three pertinent events of pregnancy failure, expulsion or need for removal for bleeding or pain. It is also true that insertion skill and follow-up experience of the physician, and the characteristics of the IUD recipient can affect these events. It follows that the influences of both the physician and the IUD wearer must be controlled for when assessing the performance of different IUDs.

**A STRATEGY FOR IUD PERFORMANCE ASSESSMENT**

The following is a step-by-step strategy for assessing a new IUD from initial consideration for testing to surveillance in service programs.

**Preclinical Examination**

Wheeler and colleagues (1974) at Battelle Pacific Northwest Laboratories have carefully documented the physical characteristics of IUDs and related these to known performance patterns with the hope of making predictions of effects of further design changes. While the performance data available left much to be desired, the approach continues to be relevant. At present, our incomplete knowledge of the mode of action of IUDs and lack of a computer data bank of large trials of several IUD designs at a few reputable centers make it difficult to eliminate IUD candidates for testing by preclinical examination. Zipper, et al. (1974), through stepwise design changes, has given us the optimal placement and surface area of copper on IUDs. There are few other examples of fruitful, well documented prospective hypothesis testing. Rudel (1974) has summarized prerequisites for admission of an IUD to trial and Sikov (1976) has defined some
of the mechanical and material properties to be considered.

**Early Clinical Trials**

There is no easy formula to guide early trials. The following questions must be considered:

1. Is this an entirely new device or an incremental change in a previously tested device?

2. What risk is there to human subjects over that of wearing a standard IUD?

3. What are the hypothesized differences in pertinent event rates compared to those of a standard IUD such as the Lippes Loop D?

4. How important are these changes as potential improvements in IUD design or as contributions to knowledge concerning the mechanism of action of IUDs?

When two or more devices are compared, devices must be randomly assigned if significance tests are to be applied to the difference between rates. Therefore, despite the extra expense, most early studies should be comparative rather than straight studies. An individual investigator making frequent sequential design changes tested in the same clinic population may appropriately use a straight study design. Such straight studies, while of value to a single investigator, do not constitute independent testing that others may rely upon. A regulatory agency may accept a straight study of a new device to satisfy itself that the device is not too dangerous to test in larger comparative
Early comparative studies of new devices against a standard device, or later studies of a modified device, should generally involve 100 subjects using each device. Trials should be conducted in more than one center and preferably with study subjects of different ages and parities. Insertions should be made by a single physician, and follow-up care should be provided by a second physician who is kept blind to the device inserted, if possible. All insertions should be postmenses, unless the device is being especially designed for post-abortion or postpartum use. Follow-up should include at least 90 percent of the study cases at the end of one year. Since pregnancy rates for standard devices are low, an improved pregnancy rate for the new device cannot be documented in these early trials, but a new device might be eliminated from further consideration if its pregnancy rate is high at all centers. At least one of the early comparative trials should measure quantitative blood loss and all should record on a calendar the days of vaginal bleeding and the degree of bleeding. This method will document any interesting differences in bleeding. Differences in expulsion rates can probably be documented from a series of small comparative studies. Expected expulsion rates and removal rates for bleeding or pain are in the range of 7 to 14 percent for standard IUDs after one year of use.

The Definitive Clinical Trial

Pregnancy and infection rates of standard IUDs are in the range of 2 to 5 percent after one year of use. Perforations occur in 0.3 to 1.8 percent of insertions. To establish interesting differences from these low rates requires large, comparative, blind trials in a few centers in populations with different age and parity distributions. At least 2000 women with postmenses insertions of the new IUD should be followed for two years with less than 10 percent lost to
follow-up per year. Regulatory agencies may decide to approve a device when one-year, stable rates are found to be satisfactory with no indication of a rise in any of the pertinent event rates. The outcome of pregnancies must be documented in all cases. Smaller comparative studies of 500 women using the new device for one year should be conducted as postabortion or postpartum insertions if the new device is to be recommended for such use.

An additional 2000 women should take part in concomitant straight studies of the new device. These studies should be done in a variety of centers with multiple inserters and different patient categories—postmenses, postabortion and postpartum. Cases should be carefully followed for at least one year to firmly establish pregnancy and perforation rates, outcome of pregnancy and difficulties in removals.

Post-marketing Surveillance

The post-marketing surveillance of IUDs is a public health responsibility to which manufacturers can contribute by longer follow-up of subjects in pre-marketing trials and by reporting rare events coming to their attention.

An important aspect of IUD surveillance is the development of an IUD data bank where information on pertinent events for a variety of IUDs in use can be stored on computer. Periodic reports of the ranking of these pertinent events and continuation rates can then be generated as suggested by Bernard in Table II. Other aspects of post-marketing surveillance are of an epidemiological nature and have been described by Kessel and Chi (1976).
THE ROLE OF THE FIELD TRIAL ORGANIZATION

A field trial organization can greatly facilitate the assessment of IUD performance, especially for new IUDs. Piecemeal assessment of IUDs can mean long delay in their development. Consider this list of steps in the development and testing of a new IUD.

1. Preclinical examination
2. Development of protocol for early clinical trials
3. Approval of protocol by a Protection of Human Subjects Committee
4. Recruitment of trial centers
5. Pretest of protocol
6. Recruitment of volunteers
7. Insertion period
8. IUD use period
9. Data collection and processing
10. Data analysis

Items 2 through 10 must then be repeated for the definitive clinical trial. It is clear that it could take two years to obtain an analysis of one year rates from an early clinical trial and that an additional 3 to 4 years may be needed for the definitive trial.

A well-established clinical trial organization can avoid delays by use of the following facilities:

1. Approved study protocols
2. A network of experienced field trial centers
3. Computerized data processing
4. Computerized data editing and query generation
5. The generated standard analysis tables
6. Experiences staff of analysts

The cycling of improvements in IUD design can then be accelerated and development costs minimized.

SUMMARY

Methodology for measuring the pertinent events used to assess IUD performance is reviewed. Factors affecting IUD performance are illustrated from field experiences. A strategy for evaluating IUDs through field trials is described, and the role of a field trial organization in accelerating IUD development is explained.
References


Table I

Title: One-Year Net Bleeding/Pain Removal Rates by Age and Parity for Selected Devices in Two European Centers.


Table II

Title: One-Year Net Event Rates* From Ljubljana IUD Baseline of Postmenses Trials.


Figure 1

Title: Two-Year Pregnancy and Bleeding/Pain Removal Rates of some Barium Polyethylene IUDs as a Function of Their Surface Area.


Figure 2

Title: The M-Device

Legend: None

Figure 3

Title: Gross Rates of Pregnancy, Expulsion, and Removal of the M-211 and M-214 Devices by Ordinal Year after Insertion.


Figure 4

Title: Gross One-Year Pregnancy, Expulsion, and Bleeding/Pain Removal Rates for the Lippes Loops B, C, and D.


Figure 5

Title: First Expulsions 3, 6, and 12 Months after 1438 Insertions of the Lippes Loop C in Four Clinics in Yugoslavia.


Figure 6

Title: Evidence of the V-Shaped Abortion Effect on Expulsion.


Figure 7

Title: Net Cumulative Expulsion Rates by Device Size and Race.


Figure 8

Title: Gross One-Year Pregnancy, Expulsion, and Bleeding/Pain Removal Rates for the TCU-200 in Two Hospitals in Bangkok.

Figure 9  Title: Median One-Year de Facto Discontinuation Rates per 100 IUD Users in 50 Studies.

Figure 10  Title: Net Cumulative Bleeding/Pain Removal Rates for the Lippes Loop C in Two Studies.

Figure 11  Title: Net Cumulative Expulsion and Bleeding/Pain Removal Rates by Religion.

Figure 12  Title: Monthly Net Bleeding/Pain Removal Rates for Early and Late Study Cohorts.

Figure 13  Title: The Pleated Membrane (IUM).
Legend: None

Figure 14  Title: Three-Month Rates (per 100 Women) of Reported Bleeding and Removals for Bleeding.
Figure 8. Gross One-Year Pregnancy, Expulsion, and Bleeding/Pain Removal Rates for the TCU-200 in Two Hospitals in Bangkok. (After Kessel, Bernard, and Thomas, 1976, reference 14.)