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Chapter 13 Preliminary studies and pilot testing

1. Introduction to preliminary studies and pilot testing

The time between the idea for an intervention trial and first entering participants into the trial is usually long, generally at least a year and often several years. Even when funding for a trial has been obtained, which, in itself, may take a year or more, there is often much work to do before the first participant can be enrolled into the trial. This chapter outlines the kinds of investigations and studies that may be carried out before starting the main trial to try to maximize the possibility that the trial will be conducted successfully. We divide these into two kinds of study. First are *preliminary studies* to develop different aspects of the trial procedures or to collect data to facilitate the planning and conduct of the trial. Second are *pilot studies* which are tests of the full trial procedures on a small sample of potential participants to make sure, in so far as is possible, that any problems with the conduct of the trial will be identified, so that procedures can be changed before the full trial starts.

Though often very useful, no specific type of preliminary study is invariably essential, whereas a pilot study should always be planned, though such studies can range from a relatively brief testing of the intervention and its evaluation that lasts a week or less through to an extensive period of testing and refinement of the intervention and evaluation methods that spans several months, or even a year or more.

2. Preliminary studies

2.1. Purposes

Preliminary studies are often conducted to refine the intervention and evaluate its acceptability, feasibility, cost, and uptake. For example, prior to a large field trial of a multi-component intervention that aimed to improve adolescent sexual and reproductive health in Tanzania, a preliminary study was carried out to test and refine the intervention. The main cluster randomized trial was planned to involve about 10 000 adolescents in over 120 schools, with an initial follow-up period of 3 years. A preliminary study was conducted to develop and refine the intervention methods that would be used to train and support teachers and class peer educators who would deliver the in-school sexual and reproductive health education intervention to be used in the trial (Obasi et al., 2006).

Preliminary studies may be needed to provide local up-to-date data, in order to calculate or confirm the sample size required for the main trial. For example, before embarking on a field trial of a malaria vaccine that will be evaluated for its effect in reducing the incidence of clinical cases of malaria, a preliminary study may be required to obtain estimates of the incidence of cases of malaria in the study population, probably spanning a complete year, in order to allow for seasonal variation in transmission. The outcome from such preliminary studies provides the data necessary for designing the size of the main trial. It is commonly found in trial design that investigators are over-optimistic about the likely frequency of outcome events in their trial population. Consequently, after a preliminary (baseline) study, the size of the main trial needs to be increased. Sometimes, the reverse happens, but not so commonly! In so far as is possible, the baseline study should be conducted under similar conditions to those that will hold in the main trial. Thus, for example, if insecticide-impregnated bed-nets are to be distributed to all children participating in a trial of a malaria vaccine, as may be required for ethical reasons, this should be done for the baseline studies to avoid over-estimating the likely incidence of malaria in the trial population (Leach et al., 2011).

In some cases, preliminary investigations may even show that the proposed study population will not be suitable. A trial of a vaginal microbicide gel to prevent HIV transmission among women in Ghana was based upon an assumption of an annual transmission rate of HIV in the trial population of 5% a year. Baseline studies were not conducted to verify this assumption, and, once the trial had started, it was discovered that the actual transmission rate was only about 1% a year. Thus, an expensive trial had to be abandoned, because of a lack of statistical power (Peterson et al., 2007). Had it been known, before the trial started, that it should have been five times as large, it perhaps would never have been started.

Preliminary studies may also be needed to estimate how long it will take to enrol the target number of trial participants, the proportion of participants who are likely to be lost to follow-up, the best interval to have between

follow-up visits, and the overall duration of the trial.

Other preliminary studies are helpful to refine the design of specific methods for use in the process and/or impact the evaluation within the main trial, and to evaluate their acceptability, feasibility, and cost. For example, will taking blood specimens, skin snips, or self-administered vaginal swabs be feasible and acceptable? Can the cold chain be maintained for vaccines or specimens that need to be kept cold, and for how long, since this will govern how frequently they need to be taken to or from the field research team? How many staff will be required, and how much will it cost, to carry out and collect data and specimens from 60 participants a day, for example?

It will also be necessary to explore the likely community acceptance of the trial (see Chapter 9), staff training needs, and other logistic requirements related to field and laboratory activities, data management, and study clinics. Some of these data may have already been collected in studies previously conducted by the trial team or by others, but, in other circumstances, special preliminary studies are required.

Many preliminary studies can be small and quick such as a qualitative study to ask potential trial participants to review a draft information sheet for clarity and acceptability. On the other hand, others may take over a year such as a study to check the incidence of a seasonal disease that must cover at least one 12-month period.

An example of a relatively large preliminary study conducted prior to a trial was the feasibility study for a multicentre trial of the impact of a vaginal microbicide on HIV incidence among women at high risk of acquiring sexually transmitted infections (STIs) that was conducted in four East and Southern African countries (McCormack et al., 2010). The main trial was planned to be conducted over several years at a likely cost of tens of millions of pounds, so it was crucial to ensure, prior to starting the main trial, that the sample size was right and that the methods planned for all aspects of the trial were both feasible and acceptable. Within the Tanzanian site for the trial, for example, a preliminary study was designed (Vallely et al., 2007). This lasted more than a year, to:

- identify the population groups to invite to participate in the trial
- work out how best to deliver the intervention and related clinical services
- evaluate the likely acceptability of the microbicide gel
- test and refine the study methods and instruments
- estimate the incidence of the primary (HIV) and secondary (STIs, reported use of the microbicide gel) outcomes for the main trial, and
- estimate the costs of each of the activities needed for the trial.

2.2. Design of preliminary studies

The design and methods used for preliminary studies should be tailored to address the specific issues and questions to be answered. Often, both qualitative and quantitative methods will be required, drawing upon social and behavioural sciences, and economic, epidemiological, laboratory, statistical, and community development approaches. Usually, a preliminary study will be relatively short term and inexpensive, in comparison to the main trial. Ideally, the main trial should be started soon after the preliminary study to avoid the situation changing between the two. This frequently raises the question of whether preliminary studies should be built into the funding proposal for the main trial, or whether they should be the subject of one or more separate preliminary funding proposals. If the latter approach is adopted, there may be a delay between the preliminary investigations and funding being secured for the main trial. A reasonable approach might be to present the design of the main trial to the funding agency, but acknowledging that preliminary studies will be necessary to confirm some of the assumptions in the proposal such as disease incidence rates. The funding for the main trial might then be made conditional on the results of the preliminary investigations. If the preliminary studies indicate that additional funding will be required for the main trial, for example, because the sample size has been underestimated, then the agency may wish to reconsider the proposal. The best strategy will often depend on the work that has been done in the past and the degree to which the results of the preliminary studies might affect the size, duration, or cost of the trial. Further details on some of the social and behaviour science methods that can be used within preliminary studies can be found in Chapter 15.

It is usually best to conduct the preliminary studies in the same general population, but in different individuals (or clusters) from those who will be involved in the main trial.

A preliminary study for the in-school intervention component of the Tanzanian adolescent sexual and reproductive health trial mentioned in Section 2.1 was conducted over a period of about 6 months in five schools that would not be included in the subsequent trial but that were conveniently located close to the offices of the research institution coordinating the trial. Teachers and class peer educators were selected and trained to deliver the in-school sessions and were then observed actually teaching the sessions to evaluate the session quality and how long it took to teach each session. The study identified misunderstandings and that there were some topics that the teachers obviously felt uncomfortable teaching, for example. Researchers also interviewed the teachers, peer educators, school headteachers, some of the students, and their parents to get their impressions of each session and the course as a whole and their suggestions for improvements. In the course of this preliminary study, many lessons were also learned about the resources that would be needed, the best ways to select the teachers and peer educators, and how to gain the trust of the local education department, school authorities, local religious leaders, students, and their parents.

The feasibility study in the Tanzania site of the microbicide trial mentioned in Section 2.1 involved conducting a rapid assessment and mapping of bars, guesthouses, restaurants, shops, sellers of local brew, and wayside food sellers, and enumeration of the number of women working in them to identify the potential numbers that could be invited to join the subsequent trial. A group of these women were invited to join a preliminary longitudinal cohort study which would receive all the proposed trial procedures, except being given either the microbicide or placebo gel. The procedures included setting up study clinics that the women were asked to attend on a quarterly basis and the regular monitoring of the outcomes that were proposed for the trial, including tests for HIV and other STIs, pregnancy, and reported sexual behaviours. The opportunity was taken to conduct comparisons of alternative ways of collecting data on self-reported sexual behaviours (including face-to-face interviews and use of pictorial diaries kept by the women) and of testing various alternative methods for interacting and exchanging information with women participants, their representatives, the owners and managers of the institutions in which they worked, community leaders, and relevant local officials. Discussions and negotiations were held with health facilities where women were referred for clinical care beyond the scope of the trial team themselves. The feasibility study also allowed detailed preparations and negotiations with national and international regulatory authorities.

Pre-testing of procedures for data and specimen collection and analysis should always be part of the preliminary studies for a trial. For example, any information sheet or questionnaire should be translated and back-translated if it is to be administered in a different language from the original in which it was designed. If it is going to be administered in several different languages, this can take a considerable amount of organization and time. The document should be pre-tested by administering it to a small number of volunteers. This will usually reveal problems with the order or clarity of information or questions, or with the coding of answers. Clearly, enough time must be left to act on the lessons learned during the pre-testing, and it may be necessary to pre-test several sequential versions of an information sheet or data collection form, before it is considered ready for pilot testing. More details on questionnaire design are given in Chapter 14.

3. Pilot testing

3.1. Purpose

Every field trial should be preceded by a pilot study (also known as a pilot test) prior to launching the main trial. This should test, on a small scale, all the study procedures, including the selection of eligible potential participants, their enrolment, recording the required data, specimen collection (if applicable), supervision systems, quality control, and data processing. If the trial involves multiple data collection rounds, where either staff or procedures change between rounds, it is a good idea to pilot test the procedures before each round.

3.2. Design of the pilot test

The design of the pilot study should be as similar as possible to the design of the procedures in the main trial, and the population selected to take part should be representative of the trial population (though not part of it). In a drug or vaccine trial, the actual interventional and comparison products (for example, drug or vaccine or placebo) might be administered, and procedures tested for monitoring immediate outcomes and responding to any potential AEs. However, sometimes, only the standard comparison product or placebo is used in the pilot study, as those included in the pilot study might not be included in the long-term safety monitoring that would be present in the main trial. For example, only the placebo gel was used in the pilot test for the microbicide trial described in Sections 2.1 and 2.2. For other types of intervention, such as the combination of in-school sexual and reproductive health education, training of

health workers and youth condom promoters, and community-wide supportive activities that were evaluated within the trial that was also mentioned in Sections 2.1 and 2.2, the interventions were pilot-tested in separate communities.

Usually, it is best to conduct the pilot study in individuals or a cluster that will not be included in the main trial, in order to avoid having to go back to the same individuals to collect similar data in the main trial. In a multi-round trial, the same specific individuals or clusters might participate in the pilot test that precedes each data collection round. This has logistic advantages. The field teams will get to know the community in which the pilot tests are conducted, facilitating logistics such as where to conduct the survey, where to stay overnight, and who the best local people are to ask to help introduce the study to householders or to help find people who do not come forward for the trial. It also has the technical advantage that the individuals and communities involved in subsequent rounds of the pilot test will have had similar prior exposure to the procedures to those in the main trial population.

The pilot study can often be linked to staff training. For example, in a multi-round field trial of vitamin A supplementation in children, staff received a specific training course that covered all the field data collection methods that would be used in the subsequent trial round. This course lasted a total of 2 weeks and included both classroom and practical training. During the first week, the practical training included ‘mock interviewing’ their colleagues and role plays, in which one interviewer asked questions of the trainer, while all the field interviewers entered the answers into the questionnaire. The pilot test was carried out early in the second week, so that any necessary changes could be made to the procedures, or even to the data collection forms, in time for the interviewers and their supervisors to be brought up to speed on the modifications before the end of the 2-week training period.

Every step in the field trial processes should be tested in the pilot study. Importantly, the pilot test of data and specimen collection procedures must allow enough time for the pilot data to be entered on to computers, ‘cleaned’, and analysed, so that these systems can also be checked for functionality. Similarly, whenever possible, any specimens collected during the pilot test should be processed, so that, at a minimum, it is possible to check that the specimens have been collected and transported correctly and are in good condition. In addition, enough time must be allowed between the completion of the pilot test and all its checks, for revisions to be made to the instruments and procedures if they are needed. All too often, inexperienced trial managers do not allow enough time for this and hope that no changes will be needed or are then under pressure to ignore indications from the pilot test that improvements would be desirable.

Sometimes, investigators are tempted to use the results from a small, time-limited pilot test to predict whether the sample size that was calculated for the main trial will be sufficient. While a small pilot test can give rise to worries about recruitment rates and suggest ways of increasing these, pilot studies will usually not have been designed with sufficient numbers or duration to give a precise enough estimate of trial outcomes to make it sensible to attempt to use it to test sample size calculations. Given very wide CIs around the outcome estimates that are likely in a small pilot test, such projections may be very misleading. If there is a need for checks on the assumptions used in the trial sample size calculation, these should be tested within a preliminary study, as described in Section 2.2.

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