Management Aspects of a Successful Community Based Clinical Trial

R. Brinda Priyadarsini, S. Sheela Devi, R.D. Thulasiraj, Dr. Praveen Nirmalan
Lions Aravind Institute of Community Ophthalmology, Madurai

"Field Trials are indispensable. They will continue to be an ordeal. They lack glamour, they strain our resources, and patience and they protract the moment of truth to excruciating limits. Still, they are among the most challenging tests of our skills. I have no doubt that when the problem is well chosen the study is appropriately designed and that when all the population concerned are made aware of the route and the goal, the reward can be commensurate with the effort. If, in major medical dilemmas the alternative is to pay the cost of perpetual uncertainty, have we really any choice?"
- Donald Fredrickson

Introduction

Rapid advances in the field of medicine have not translated into adequate changes in the health indices of the developing world. Health-related issues have not been adequately addressed on a population basis for many reasons including, lack of resources. Medical practice in the developing world is often guided by primary research conducted in developed countries. This relationship is problematic, however, because the population that has been studied may not be representative of that on which the study outcomes are practiced. Current research activities are hampered by improper design, lack of planning for outcomes, inadequate dissemination of information and unreliable or invalid data. Community-based health studies have large sample sizes and must be effectively managed to ensure accuracy, validity and reliability of the data. Since community-based studies are resource intensive, and given that most developing countries are strapped for resources, effective management is particularly important in ensuring that resources are conserved.

This article discusses guidelines to conduct a successful community-based clinical trial in the developing world. Well-designed studies on issues related to health in developing countries are essential to plan for effective health interventions and programmes.

Definition of clinical trial

A clinical trial is an experiment designed to assess the efficacy of a test treatment by comparing its effects with those produced using some other test or control treatment in comparable groups of human beings**.**

Pre-study phase

The success of the research study is determined by the planning that precedes it. The first step in formulating a research study is to frame a research question that is relevant to the health needs of the population being studied. The study should contribute to and build upon already existing knowledge. Once a pertinent research question is identified, long-term goals and specific aims for the study are determined. The results may be measured through various outcomes what these outcomes, are and how they will be measured must be decided upon before the study is begun. The study design is chosen by considering what format will best address the question and reveal the outcomes in a cost-effective manner. The population to be studied must be characterised: the number of persons to be studied and eligibility criteria for both inclusion into and exclusion from the study has to be determined; care must be taken to ensure that the study population is representative of the general population and that

there has been no selection bias while excluding any segment of the population from the study. Finally, the intervention strategy must be determined to optimise results from the study.

Prior to beginning the study, the researcher must have the study approved by the institutional review board. This is a committee consisting of various pre-selected eminent personalities who review the study protocol and decide if there are any ethical issues in conducting the study. It is also necessary to obtain permission from the local administrative bodies, and perhaps even from the state or national governments, as well as the state or national medical research committee.

Logistics planning

Study material

Study materials are the physical items used by study centres and may include protocols, documentation of decisions and operations, data collection forms, training materials, operational manuals for resource centres, drugs, preprinted labels, computers and software.

The study protocol is the most important document because it specifies the goals, rationale, organisational structure and data collection requirements of the study. Typically, all disciplines required for the conduct of the study are considered in the protocol development process. The data collection process must strictly adhere to the procedures laid down in the manual of operations.

Drug distribution

The distribution of drugs during the study involves bottling, labelling and inventory control. Utmost care should be taken to check the expiration date and potency of the drugs at frequent intervals. Drugs should be stored as per the standard set by the manufacturer. Preparation of matching placebo medications is a technically complex yet critical element in masked studies. A separate system should be introduced for monitoring the safety of drugs used for intervention.

Field logistics

Infrastructure

The infrastructure of the study - including the field office, stock room, vehicles, computers, files, and racks – should be built in advance. Furthermore, field workers must be assigned to their respective areas. Division of the study area (in clusters) provides for better distribution of work. Accordingly, supervisory staff should also be assigned. It is advisable in research projects to have several levels of supervision in order that high quality in data collection be ensured.

Designing of forms

The design of data collection forms should take into consideration the objectives of the study, the outcome measures, and what data are necessary to obtain reasonable results. One should also ensure that the forms are designed such that even secondary data (related data) are collected. It is always advisable to collect baseline details, such as household census, literacy level, and socioeconomic status, to have an idea of the demographic characteristics of the population under study.

Once the type of data to be collected is determined, it is important to use staff who have the knowledge and experience to create an appropriate and effective layout for the questionnaire. The following elements should be considered in framing questions:

- They should be clear and concise
- Should produce consistent results
- User-friendly as well as data-friendly
- Closed questions are generally preferred, although it might be necessary to phrase open-ended questions for some studies.

The designed questionnaire should be pre-tested on a small sample to assess:

- Ease of application
- Whether questions follow a logical order
- Level of difficulty for the subjects being tested
- The method of questioning
- The effects of interviewer bias

Based on the feedback from the pre-testing, the forms may be modified and finalised. The pre-tested data may also be used to refine the data entry programmes.

Pilot study

The purpose of a pilot study is to guide the development of a study protocol that will produce better answers to the research questions in a cost-effective manner. The main objective is to test the

feasibility of the methodology and to plan the logistics. It can also determine data collection methods. Pilot studies play an important role in testing the systems for data management.

Community preparation

It is the most important stage before the implementation of the project. The success of the project mainly depends on the efforts taken to prepare the community to understand the project, its importance, and their role. The first step is to meet with the village local leaders and panchayath presidents to explain to them the need for the project in that community and to seek their cooperation. Government officials, such as district health officers, primary health centre staff, other nutritional service providers and private medical practitioners, ought to be met separately for their cooperation and support. If possible, clear guidelines of their expected role in the project should be provided.

The next step is to meet with the community in which the project will be conducted. This can be done through a series of meetings and gatherings at the village level. The group may be the potential participants, local leaders, and panchayath officials. For example, if the study is focusing on women, local NGOs as well as organisations like mahalir mandram, traditional healers, self–help groups, dhais and nutritional service providers can be invited for better participation.

The main focus of the meeting should be to address the following:

- Reasons for selecting the population
- Risks and benefits to the community
- Objectives and methodology of the intervention
- The study population's role, involvement and participation
- Staff introduction
- Informed consent

As a part of community preparation, field workers may be asked to enumerate households to develop individual relationships with members of the community. Addressing the community in this manner also serves to gather baseline information on people in the study.

Organisational structure development

Organizational structure is essential to ensure smooth functioning of the project. Persons responsible for various activities must be identified; delegation of authority is important to ensure that someone is centrally responsible for the overall functioning of the project. The decision making process should be clarified.

Development of the organisational structure is dependent upon the workload involved in the study as well as the size of the study. For example, if a particular study covers a population of one hundred thousand or more (as in a block), it might be advisable to have an office in the field manned by an officer and support staff. This is necessary to ensure that problems that arise during the study are addressed in a timely fashion. If for a particular study the villages are scattered, it might not be cost-effective to have a central field office; rather, it may be more viable to have the supervisory staff reside in the village for the duration of the study or, if possible, to recruit supervisory staff from the village.

Example: A study of Vitamin A Supplementation in Newborn (VASIN) children was a double-blind, community-based, large clinical trial conducted over 3 years. It tested the efficacy of vitamin A in reducing infant mortality rates. The sample size was 9000 live births, among a population of 250,000, which were

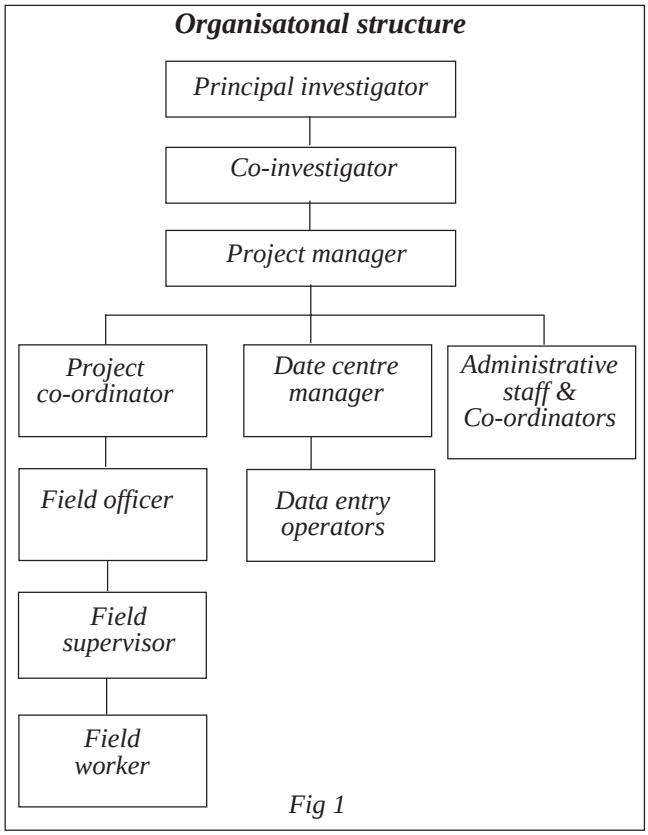


Fig 1

given doses of the vitamin and followed for 6 months. More than 100 workers at various levels were involved in the project. Fig 1 shows the line of command and reporting system of the staff in the project.

The line of command was framed in such a way that the flow of communication was disseminated from top to bottom. Any information regarding the data collection was set up to flow from bottom to top. Regular weekly and monthly meetings at various levels were organised to collect and disseminate information.

Committees that facilitate smooth functioning of the study and adequate dissemination of results are important to a research study. The following are examples of such committees.

1. Executive committee (EC)

This committee maintains scientific and administrative responsibility for the conduct of the research study. It approves all changes to the protocol and decides issues related to financial and administrative aspects of the study. It also serves as the publications review committee; all publicity, presentations and manuscripts from the study must receive approval at this level. Members meet regularly; the frequency of these meetings is based on the needs of the study. The investigators and co-investigators form the members of the committee

2. Steering committee

The dominant scientific leadership committee often is called the steering committee. This committee directs the EC. They develop and test all necessary study forms and procedures, and produce a manual of operations that documents these procedures as well as the methodology of the project. This committee makes recommendations to the EC regarding any proposed additions or alterations to the study protocol. The steering committee meets on a regular basis, and their schedule too, is determined by the requirements of the study.

3. Data and safety monitoring committee (DSMC)

Data and safety monitoring committees play an essential role in the conduct of clinical trials. This committee usually is composed of external medical research experts, such as biostatisticians, and may also include persons not related to health care. This committee provides external objective advice to the executive committee regarding the safety and efficacy of the intervention being tested. They are responsible for reviewing the study data on a regular basis, summarising their conclusions and advice in a written set of minutes, and communicating this information to the executive committee. They have a specific responsibility to determine if there are problems related to the safety of the intervention such that the trial should be stopped or to determine whether the study should be stopped early because the benefit of the intervention has proven to be stronger than originally anticipated. The schedule of DSMC meetings is based on the duration of the study and the nature of the proposed intervention as well as outcome measures. If two or more interventions are being studied, the results are discussed in the DSMC without breaking the masked nature of the study. The members of the DSMC are not aware which results belong to which intervention group; they are only aware that one intervention has a particular result and the other has another result. Members of the investigative team are not allowed to vote during the DSMC meetings but may take part as non-voting members as long as they do not become aware of the specific groups of interventions that produce specific results. For example, if treatment A is being compared with treatment B, the DSMC will see the results only as group 1 and group 2. They will not be aware of which of these groups received treatment A and which of these groups received treatment B; this blinding ensures that there is no bias while discussing results. The DSMC can decide on breaking this masking after a vote, although this measure is usually taken only if there is a marked disparity in the results, such as when one intervention is found to be markedly beneficial or harmful.

4. Local advisory committee

This committee gives advice on local operations in the field and on other aspects concerning how the study is conducted. Prominent members of the medical field and leaders of local volunteer agencies may serve on this committee. The panel meets whenever the project staff needs independent advice on some aspect of the study process.

Manpower planning

For any large community-based clinical trial, it is important to plan the number of workers required in each category, their job description and training needs, and the process of their recruitment and selection.

Following are the variables to be considered in deciding the number of field workers:

- Field work should not exceed 6 hours per day (excluding travel)
- The number of villages or the number of subjects to be covered in a day
- The distance to be covered by the field worker

Job description

Any community-based trial needs a large workforce for its implementation. The size of the workforce mainly depends upon the nature of intervention and data collection. The management of the personnel involved is a challenging and difficult task. A clear organisational structure and clearly defined positions enable better management. The following are integral components of a well-defined job description:

- A clear statement of the responsibilities of the individual in the project.
- The methodology involved in performing the required activity.
- The name of the person to whom he reports, the frequency of reporting, and the medium of reports —i.e., whether the reports should be oral, written, or a combination of the two.
- The nature of job — i.e., whether it is permanent or temporary, scheduled hours, salary, and other benefits.

Recruitment and training

The following guidelines may be helpful in selecting various levels of staff:

Supervisory staff

- Basic qualification – graduation
- Minimum years of relevant experience
- Supervisory capacity
- Leadership, team-building and problem-solving skills
- Willingness to reside in the supervisory area

Field personnel

- Chosen from among the study area
- Meet certain qualification criteria
- Are familiar with the area as well as the people and their usual practices and beliefs.
- Have a good rapport with members of the community and good reputation in the village.

It is advisable to select the field personnel from the cluster to be studied because they are familiar with the community. They can therefore ensure better community participation, and facilitate smooth functioning of the project.

Administrative staff

For any institution based community research project it is favorable to use the existing staff for administrative duties, such as accounting and storekeeping, as their involvement in the study will be limited. This is highly cost-effective for any research study.

Training

Personnel are trained in order that uniform procedures are followed. Study procedures can be ineffective if the people who apply them are not properly trained. Before beginning a training programme, the duration, content, methodology of teaching, faculty, and venue should be finalised. The main objective of the training programme should be to make the project staff understand the objectives of the study, its methodology, the need for the study, and their respective roles. The training should focus on the practical aspects of planning their work, scheduling, and prioritising their activities and reporting pattern.

The design of the training programme should equip the staff with the skills to face the challenges in the community. The programme should be practice-based; it can take the form of games, role-plays, and exercises. Individual attention should be paid to all the field staff. Feedback should be used in evaluating them. The training should inculcate attitudinal change among staff to accept the value of research studies and to act with honesty and integrity in data collection. Interactions with senior research professionals in the organisation can facilitate this attitude.

Intervention management

This is an important phase in a research project; to a large extent, it determines the success of any well-designed study. Despite adequate training, staff may face problems with planning, scheduling, completion of forms and co-ordination. A monitoring system must be evolved during this stage to facilitate field activities and to guide the staff in problem solving. For example: frequent field visits by supervisory staff to assess the quality of work done by the field personnel. Such assessment may include verification of the data collected, verification of the registers and logbook for completeness, and monitoring of time schedules, adherence to tour plans and community involvement through feedback from the community.

When the assignment of treatment is masked to the study participant or to the study investigator, there must be special mechanisms in place to assure that the correct treatment is provided to the study participant.

Managing randomisation

Random assignment of participants to treatment options, and masking of the researchers and participants to this assignment, plays a vital role in the ethical considerations of any community-based clinical trial. This method is employed in order that all participants in the study have an equal chance of getting any intervention strategy. As an ethical measure, staff involved in the project should not influence the randomisation procedure. Thus those directly involved in implementation should be blinded to the intervention. In order to maintain the integrity of the project, a properly designed randomisation system must be developed based on the nature of the study.

For example, in a cohort study looking at the effects of the Antioxidants in Prevention of Cataracts (APC), (a double-blind, placebo-controlled trial with a 5 year follow–up), the treatment code was assigned to the subjects at the beginning of the study by the data centre.

In another example, the VASIN study, the randomisation had to be decided in the field. In such a situation a pre-randomised list can be generated, which the workers follow in a sequential order. Any problem encountered in this process should be brought to the notice of the principal investigator whose decision on the matter in question is final. Even though the workers have been masked to the intervention, they may be subject to natural human curiosity to unmask or fiddle with the randomisation strategy. This possibility must be addressed by creating an attitudinal change among the workers. Any suspicion in the assigned treatment among the subjects should be excluded for data analysis. A strict monitoring system should be adopted to check whether the subject is receiving the intervention as per the randomisation.

The creation of randomisation materials requires careful planning under the supervision of a statistician.

Ethical considerations

Ethical considerations are fundamental to the design of any research investigation involving human subjects. Three primary ethical principles are:

1. Respect for persons – Treating the subjects as individuals and obtaining their informed consent for their participation in the study.
2. Beneficence – Protocol should be designed to provide valid and applicable knowledge to maximise any benefits and minimise any risks for the subjects. Both the risks and benefits of the study must be indicated to the subjects in procuring their informed consent.
3. Justice – Benefits and burdens of research must be distributed fairly among the population.

Safety of the subject should be the prime concern in any trial involving human beings. A free clinical service should be provided to the subjects for any discomfort caused by the study.

Monitoring systems

Monitoring of personnel is important in evaluating the effectiveness of training and dissemination of information. On-site observation may be necessary to confirm that the individual performing the procedure understands the instructions and is able to implement them satisfactorily.

The project manager must be thoroughly familiar with all aspects of the study protocol. He/She must be highly motivated, exercise mature judgement, and employ excellent interpersonal skills. The needs of the study must be carefully considered to assure that training and monitoring priorities are consistent with overall study goals.

Refresher training

The major portion of training activity often takes place at the beginning of the study. It is almost always necessary to plan for continuing training because of the inevitability of field site staff turnover and because of changes in procedures that may be required as the study progresses. Many large community-based clinical trials are conducted for 2–3 years. To retain the interest and participation of the field staff intermittent refresher training courses should be organised. This review enhances the knowledge of the staff about the project. Intensive training may be provided based on the lacunae in performance. The first refresher training should be planned within 3 months of the intervention to avoid any ambiguity in the procedures.

Field activities

Planning and scheduling of activities

Fieldwork is usually scattered among villages. Since it does not follow the rigid structure or schedule of an organisation, it is more difficult to manage. The schedules of fieldwork are highly dependent on the predominant occupation of the people living in the community. The worker needs to plan and schedule his/her fieldwork based on the participants' availability. The project manager should guide the workers in planning and scheduling their activities. Accordingly, the field workers are appointed as full-time or part-time staff. The work planning should mainly focus on the following:

- Priority of the activity
- Grouping of work activities in a single visit
- Adherence to time schedules
- Details of informing the changes in work plans

Depending on the workload, a weekly or fortnightly work plan may be decided. Supervisory staff plan their visits based on the field staffs' plans. Effective planning and scheduling enhances the quality of work and paves way for developing better monitoring systems.

Supplies

Timely supply of materials smoothes the flow of field activities. If the office has enough space for storage, it is advisable to purchase materials in bulk to avoid problems in procurement. To avoid pilferage and for better management, a proper system of registers to monitor receipts and issues at various levels should be maintained. Verification of proper bookkeeping should be done at regular intervals to assess the system. It is necessary to maintain a 3-month inventory of all the items required for the study.

Performance review

In any community-based clinical trial, the work of the field staff tends to be monotonous. The lack of change affects their performance level and increases the staff turnover. To retain and motivate the morale of the staff, work performance should be reviewed at regular intervals. This evaluation can serve as a basis for salary increments and other benefits. Social gatherings and luncheons may be arranged to encourage participation and involvement.

Communication network

There are two primary units in any community-based clinical trial, the organisational unit and field unit. To create a link between the two that will avoid gaps in the flow of information, it is necessary to establish communication networks. This connection can be achieved through organising weekly and monthly meetings at the head office to review the field activities and the performance of the field staff. Within the field, it is particularly important to establish a network because of the complexity of the work, the number of people involved, and the necessity to make quick decisions in the community.

For routine planning, review of activities and sharing of information, weekly meetings can be conducted in the respective field areas. Messages regarding changes in work schedule can be conveyed through the selection of a place frequented by most people, such as a balwadi, PHC, or a shop. This system ensures a smooth flow of communication and enables the supervisory staff to monitor the work and staff, without any delay in decisions.

Follow –up activities

Follow–up concerns the tracking (coverage) of the subjects in the study. It can range from monitoring compliance to recording the impact of the intervention over a specific period of time.

It depends mainly on:

- Community participation
- Monitoring systems

- Motivation or interest of the staff
- Knowledge of the study area

A system should be designed to monitor variations in the tracking (coverage) at the individual level. Sufficient measures must be taken to avoid for low coverage and alternative-tracking methods can be planned accordingly.

Example: In the APC study, which has a 5-year follow–up, maintaining contact with the subjects for yearly follow-up is an important to evaluate the treatment effect. Community meetings were organised at regular intervals to create awareness about the importance of members' participation and involvement throughout the course of the study. This method helped retain the interest of the participants in the study.

Migration

For any community-based clinical trial, migration of the subjects for occupational and other reasons should be considered in the follow-up activity. Theoretically, a 10% attrition rate in the total subjects is assumed for a study. If in any area migration exceeds beyond this limit, it has to be probed. If necessary, information, such as vital status, can be collected from a secondary source, such as relatives, for data analysis. However, clear guidelines have to be in place to ensure the reliability of the data to be collected.

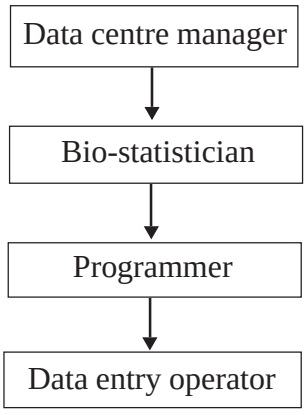
Quality assurance

Quality control is an important aspect of clinical research. It should be present throughout the study; it begins at the design stage when approval is attained from the ethical committee and government bodies and standards in intervention are set. In the implementation stage, quality should be ensured in data collection and management, staff performance and laboratory procedures. Experiments that use drugs, particularly those that are blinded, require special attention to the quality control of drug intervention. Periodical tests of potency and expiration should be run. Care should be taken to store the drugs as per the prescribed standards. In data collection, quality should be considered from designing the form through recording and storage of data. Setting up standards for monitoring and maintaining quality control throughout the study is solely the responsibility of the project manager.

Data management

Data management plays a vital role in any research study. The data management system developed should minimise the gap between data collection and entry. It is ideal to collect and enter the data concurrently, although this is not always possible. It is advisable to finish entering the data of one set of information before collecting the next data set to ensure accuracy. The outcome of the project depends largely upon the quality of the data collected. Equal emphasis has to be placed on collection and storage of data. The department must be equipped with the required facilities and manpower. As the volume of data collected in large community-based trials is huge, the system should be equipped to accommodate all the data and have backup facilities. Furthermore, there should be protection against corruption of files; utmost care should be taken to store the data. The department manager should be well trained to develop programmes for data cleaning and report generation and should give guidelines to the project manager to facilitate the fieldwork.

Example: In a Vitamin A supplementation study, reminder dates for follow-ups were generated by the data centre, based on enrollment. Data may be entered either at the head office or in the field. The site chosen mainly depends upon the complexity of



the data collected. Example: In rapid assessment survey the data entry is done concurrently with data collection, in order that any error in collection can be rectified immediately without compromising accuracy.

Structure

Even if we use the institutional manpower (employees of the organisation), it is highly recommended to assign personnel to a particular study. The data centre can enhance the quality of data by designing the following programmes:

- Control checks to detect errors at the time of entry
- Double entry system to eliminate operator error
- Formation of a flow system designed in a manner that minimises time between data collection, entry and error detection and correction
- Filing systems for easy retrieval and proper maintenance of forms
- Data cleaning programmes and analytical programmes
- It is always advisable to make a photocopy of the error form for corrections made in the field

Study administration

Cash flow monitoring

Most research projects are carried out with the help of external grants or funding. To sanction the research the implementing agency should submit a framework of expenses for the study period. This framework should be based on the expenses to be incurred for the activities involved during the course of the study. It is mandatory to provide justification for the estimated expenses.

In order to remain within the budget it is crucial to develop monitoring systems for effective utilisation and tracking of funds. A cash flow statement, wherein the increase or decrease of expenses against the budget for each category is noted, can track expenses. Based on this, necessary cost control measures can be adopted. A periodical report of the expenses must be submitted to the funding agency with the status report for better coordination and support.

Personnel functions

Unlike an organisation in which people work under one roof and are easy to manage, field staff are scattered among villages and are difficult to coordinate. There should be some mechanism to manage and coordinate the workers. As in an organisation, a duty roster should be followed for the staff involved in the project. This inculcates discipline and enhances the morale and a sense of belonging with the organisation. It also forms a basis for salary calculation. At the time of appointment the staff should be informed of their leave eligibility and the procedure involved in taking leave. Proper mechanisms must be set up to make alternate arrangements in the field in case of absence to avoid disruption in work.

Outcome measurements

The following are some of the indicators to evaluate the outcome of the study:

- Treatment effect
- High response rate – it can be either high compliance or high follow-up
- Less loss to follow-up
- Dissemination of information, either as presentations or publications

Conclusion

Conducting community-based clinical trials is more complex and expensive than routine hospital-based studies. A well-planned and monitored study, however, will yield valuable results that may pave the way for framing policies in prevention of diseases. Care must be employed at all stages of the study to ensure that results obtained are valid.