CONTROLLED CLINICAL TRIALS IN TUBERCULOSIS

A Guide For Multicentre Trials in High-Burden Countries
2004

International Union Against Tuberculosis and Lung Disease

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I. INTRODUCTION

Randomised controlled trials (RCTs) have long been recognised as the gold standard for assessing the efficacy of new interventions. Properly conducted, they are designed to eliminate selection bias, which may otherwise confound the results of an investigation.

The trial of streptomycin versus bed rest for the treatment of tuberculosis, undertaken by the British Medical Research Council (MRC)[1] is widely recognised as the first trial undertaken which conforms to modern standards; it resulted in one of the most extensive series of clinical trials ever undertaken for a single disease. These trials played a significant rôle in identifying currently-used chemotherapeutic regimens for the treatment of tuberculosis, which have achieved high rates of cure with low levels of toxicity.

The earliest trials in tuberculosis involved treatment using only a single drug (monotherapy). Subsequent studies, with two- and three-drug combinations quickly established the efficacy of multidrug chemotherapy in achieving successful treatment in a disease which had, hitherto, a high fatality rate. Further trials established the strategy of the initial intensive phase of treatment with three or four drugs, followed by a continuation phase of two drugs. RCTs have also demonstrated the efficacy of domiciliary treatment, as compared with treatment in an institution.[2]

A significant disadvantage of the regimens developed in the early 1960s, was the minimum duration of treatment of 18 months which led to a breakdown in compliance of both patients and the treatment services resulting in major challenges to achieving successful treatment.

With the advent of rifampicin and the revisiting of the role of pyrazinamide, it was possible to reduce the duration of chemotherapy to 6 months, as demonstrated by the British Medical Research Council through RCTs carried out in East Africa, Hong Kong and Singapore.[3-5]

However, in spite of these advances, tuberculosis remains a disease exacting a heavy burden to health and to the economy in low income countries, the problem being further exacerbated by the HIV/AIDS epidemic, both conditions imposing an ever increasing burden on the economic as well as the administrative capabilities of these countries.

If these burdens are to be overcome, further RCTs of new drugs will be needed. The development of new compounds requires testing in large-scale trials through the rapid recruitment of large numbers of patients in order to progress logically and to have timely results. Such large-scale trials can only be carried out if a substantial number of centres are engaged. Moreover, to establish the generalisability of results under different genetic, social and behavioural conditions, trials need to be conducted in settings involving the participation of centres in many countries worldwide.

II. HISTORICAL PERSPECTIVE

A trial to find a cure for scurvy was conducted in 1753 by Lind, a ship's surgeon, in which he attempted to divide the trial subjects into two similar groups, thus creating a control group. He writes:

"I took twelve patients in the scurvy on board the Salisbury at sea. **The cases were as similar as I could have them ...** they lay together in one place ... and had one diet common to them all. Two were ordered a quart of cider a day, two took 25 gutts of elixir vitriol, two took two spoonfuls of vinegar, two were put on a course of sea water, two others had each two oranges and one lemon given them each day and two took the bigness of a nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons…".[6]

Although in Lind's trial the treatments appear to have been randomly assigned, a trial to evaluate the use of penicillin to treat infected soldiers during the Second World War, made no such attempt and no control group was included. The author writes: "Clinical trials began with very few extremely ill patients due to shortage of drug. ….. Such dramatic results were seen that the lack of controls did not seriously impede clear conclusions."[7]

By present standards, each of these trials had one or more deficiencies in their design. The first trial, in which the randomisation schedule was properly concealed, was the Medical Research Council's trial of streptomycin in the treatment of pulmonary tuberculosis, the results of which were published in 1948.[1] Because the demand for streptomycin far exceeded the amount available, it was decided that the best use of the drug would be through a randomised trial. Randomisation relieved clinicians of the responsibility of deciding who should be treated. By its design and method of conduct the streptomycin trial served as the gold standard for future trials.

This landmark study was followed by an uninterrupted series of clinical trials in tuberculosis by the British Medical Research Council which continued for 40 years and which ultimately led to the demonstration of highly effective short-course chemotherapy.[9]

RCTs are now accepted in all branches of medicine and are used not only to assess new drug therapies but prophylactic regimes, surgical interventions and health policies.

III. WHY DO WE NEED RANDOMISED CONTROLLED CLINICAL TRIALS?

As mentioned, in the Introduction, randomised controlled trials (RCTs) have long been recognised as the gold standard for assessing the efficacy of new interventions. By **randomisation** is meant the allocation of the patients to treatments being studied in a random way, where neither the doctor, nor the patient, knows what the treatment will be before the point of its allocation. The reason for this is to eliminate **selection bias** by which is meant the conscious or subconscious selection of study procedures (type of patient, certain investigation) that depart from the criteria laid down by the protocol.

A **controlled trial** involves the inclusion of an established (or placebo) treatment against which the new intervention is to be evaluated.

There are other ways we might consider for comparing two treatments than going to the trouble of setting up a trial. Unfortunately they are all flawed in some way or other.

- Supposing we were to compare patients treated for a disease with those not treated. Common sense tells us that there are very likely to be important differences between these two groups of patients. Those not treated may be less ill, or possibly in some cases too ill to treat. Treatment is never given at random.

- Another approach might be to compare treatment at one hospital with that at another. The problem here is there are likely to be more differences between the hospitals than simply the two approaches to treatment. The characteristics of the patients may well differ and the type of care could differ as well.

- A third approach is to use what we call historical controls. Sometimes this is unavoidable but it has the potential for serious biases. Patients and their prognosis may both differ over time, management will almost certainly differ and the historical data is less likely to be complete than data collected prospectively.

All of these contrasts are imperfect in one way or another. Very occasionally we can demonstrate a drug to be highly effective without any controls at all; this was what happened with penicillin when it was first tested in soldiers in North Africa during World War II. Such circumstances are exceptional. In general, studies without controls are impossible to interpret.

An example of an unsatisfactory non-randomised comparison is an unrandomised assessment of hormone replacement therapy (HRT) in women. As there are likely to be important social differences between those taking HRT and not taking it, this will result in a very biased comparison. Thus, the randomised trial is essential to obtain an unbiased result.

We can rarely exclude selection bias from observational data. Sicker patients are likely to be prescribed more potent drugs and in some circumstances there will be limitations due to the availability of drugs. Even if we attempt to adjust for all the differences we know about there will almost certainly be some of which we are unaware.

A recent paper reported on the results of two comparisons of different antiretroviral drugs given to similar groups of patients. In one comparison patients were randomised; in the other the doctors decided which drug to give. The results were strikingly different. In the randomised comparison drug A was significantly better than drug B and in the doctor's choice comparison drug B was significantly better than drug A. It was impossible to determine the reason for this difference.[9]

Even conducting a randomised trial will not necessarily answer all the questions we may need to answer. Because a drug works (or does not work) in one population does not guarantee that it will work or not work in a second population. Recently recommendations were made about giving prophylactic treatment to patients with HIV and TB based on one study in West Africa. Countries in East and Southern Africa were reluctant to adopt these recommendations without more evidence since the profile of resistance to the antibiotic used in the trial was very different according to location.

It is also true that giving the same drugs but at a different disease stage may result in very different outcomes. This was most clearly illustrated with zidovudine which, although shown to be highly effective in patients with AIDS,[10] did not delay the onset of AIDS and/or death in those with asymptomatic disease.

Trials may often need to include a long term follow-up, sometime very long. The MRC WISDOM trial of HRT was designed to follow women for 10 years.

Early results from a trial may be misleading and not give the whole picture. A trial of preventive therapy for TB in patients with HIV infection in Zambia

showed very promising short-term results but long term follow-up showed that these benefits diminished with time.[11]

As treatments get better and patients survive longer trials need to follow-up more and more patients for a longer and longer time to establish whether one treatment is superior to, or as good as another. If we could find a surrogate for long-term outcome it would enable us to avoid having to do very long trials. A possible surrogate in TB chemotherapy would be the 2 month culture result.

A good surrogate must be 1) an event early in treatment, 2) an event predicting long term clinical response and 3) the occurrence of that event should predict response regardless of the treatment being assessed. The 2 month culture result meets the first two of these conditions but not the third, which is always the most difficult one to satisfy. We need to continue doing trials and in TB follow-up should be for at least 12 months after stopping treatment by which time a very high proportion of relapses will have occurred by that time.

IV. AIM OF CONTROLLED TRIALS

Eliminating bias

The main objective of a clinical trial is to ensure that the comparisons made are convincing and informative. Fundamental to doing that is the avoidance of bias. The assigning of patients to treatment by a process of random allocation is the backbone of this process. Bias can occur in several ways; these include the methods used in handling of the randomisation, the lack of a clear hypothesis with accompanying endpoints, the procedures for assessing outcome, failure to publish negative results.

Randomisation ensures treatment allocation is left to chance, BUT it does not guarantee that patients in different groups will be similar in all respects. Reliable conclusions about an intervention can only be drawn if the groups to be compared are, as near as possible, identical in all respects upon entry to the trial. Randomisation of a sufficiently large number of individuals helps to ensure comparability between groups with respect to known and unknown characteristics which may influence outcome.

- **At allocation:** It is no longer regarded as acceptable that allocation to an open label or single blind design study should be determined by opening the next in a series of envelopes held by the local investigator. Telephoning an independent office is preferred; - if envelopes are used they should be held by a person independent of the trial.

- **During the trial:** Clinicians agreeing to take part in a trial should be in a state of equipoise regarding the hypothesis to be tested. If a clinician is convinced of the superiority of one of the study treatments it is inappropriate for the clinician to take part in the trial. All patients should be treated in an unbiased way without regard for the treatment they are receiving. To achieve this will sometimes require that a trial is of a double blind design.

- **Through loss to follow-up:** Patients lost to follow-up are unlikely to be typical of those who remain. A high loss to follow-up can seriously distort

the outcome of a trial. Supposing a new drug has unpleasant side-effects; if patients with side-effects stop taking their treatment and stop attending, those remaining will represent only those who can tolerate the drug.

- **In assessment of endpoints:** Every effort should be made to ensure that assessment of endpoints is never influenced by knowledge of the allocated treatment. This is particularly true if there is any element of subjectivity in the assessment such as symptom scores or radiographic changes.

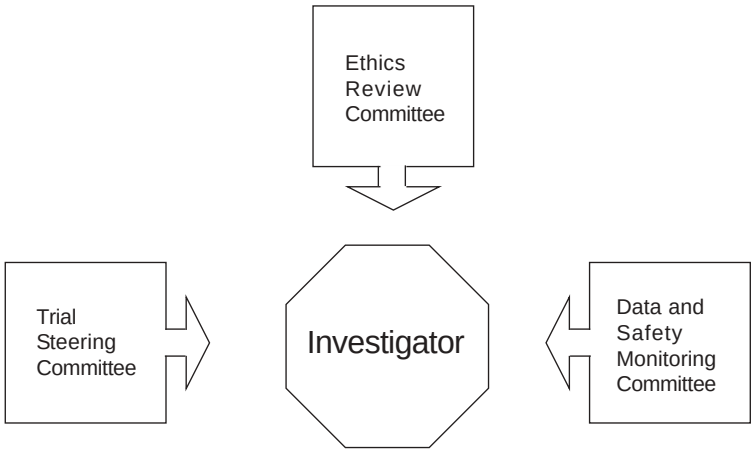
- **In publication, or lack of it.** Journals are often less than enthusiastic about publishing results of negative studies. However, when only positive results are published it is quite likely that wrong conclusions will be drawn about a new intervention. Meta analyses must include all relevant studies whether published or not.

V. DESIGN ASPECTS

Framework for trials

All trials should be governed by a team comprising several bodies as shown in the diagram below. The central body, the investigators, are responsible for the development of the protocol and conducting the trial until the final publication of the results. All the committees have input into the protocol, each operating independently of the other.

The terms of reference of each committee are described in **Appendix IV.**



Standard Phases in the evaluation of drugs

Any new drug, demonstrating good *in vitro* activity, which can be confirmed by animal studies, must be tested in four phases of clinical trials.

Briefly, the four phases are:
Phase I: The establishment, usually in healthy volunteers, of the pharmacokinetic and, where possible, the pharmacodynamic profile of the drug.

Phase II: This is a pilot study in patients suffering from the disease for which it is intended. The aim is to determine the therapeutic activity and short-term safety

of the drug. The results may, if necessary, be confirmed by placebo-controlled design, although such trials would not be relevant for diseases like tuberculosis where established treatments exist. This phase can also be used to establish dose ranges and dose/response relationships.

Phase III: This phase is a large scale RCT usually involving hundreds or even thousands of patients that aims to establish the (short and) long term safety and efficacy of a drug. It is also used to determine the overall therapeutic value of the drug as well as the pattern and profile of any adverse reactions.

Phase IV: Drugs that have been licensed for use can enter Phase IV or post-marketing studies. Post-marketing studies of two types are required, namely evaluations of new drug treatment outcome in regimens which differ from the standard on account of local policy, and surveillance in different populations of drug resistance and adverse effects related to the new drug. The primary treatment outcome variable will remain the same as in Phase III trials. However, patient acceptance of the new drug must be objectively assessed, in order to provide national programmes with the assurance that it is financially worthwhile and in public interest to change to a new drug or regimen in the public health service.

The purpose of this guide is to inform trial participants on the steps involved in randomised controlled clinical trials, that is, Phase III and Phase IV trials.

Conduct of clinical trials

A well conducted clinical trial must follow well defined steps in order to arrive at a valid result. These are :

1. Initial design and protocol development
2. Ethics Committee review
3. Patient recruitment
4. Treatment phase
5. Follow-up phase
6. Data analysis
7. Publication of result

The protocol

A well-designed trial will have a protocol, which sets out in considerable detail every aspect of the trial. The protocol will usually contain the following sections:

- Background and aims
- Specific objectives
- Trial design
- Eligibility criteria (including those ineligible)
- Trial endpoints
- Randomisation procedure
- Treatment/intervention details
- Assessment of endpoints
- Follow-up procedures
- Statistical considerations including outline of analysis plan
- Procedure for handling adverse events, in particular serious adverse events
- Committee membership
- Appendices, including patient information sheet and consent form

In addition, the protocol should, if possible, set out how missing data will be handled; this issue is addressed in more detail in section VI on "Analysis of data".

If scientific research is undertaken in the absence of a comprehensive protocol, there may be a temptation to modify the procedures and change the assessment criteria at the time of analysis in order to achieve a particular result.

The protocol represents a detailed operations manual for the trial. Alongside it there should be detailed operating procedures, commonly referred to as standard operating procedures (SOPs), which provide specific instructions for activities such as laboratory methods, the data collection and quality assurance aspects of the trial.

The process of development of protocols is described in detail in the book: 'Research Methods for the Promotion of Lung Health' published by the IUATLD[12] and available on the website www.iuatld.org.

Trial justification

A clinical trial is a planned experiment carried out to evaluate the efficacy of a specific treatment in human subjects. The trial is usually done because of the

need to evaluate the efficacy of a new treatment. Before embarking on a trial it is important to establish the need for the trial in the light of all the available data, published and unpublished. This may entail performing a systematic review of relevant studies.

Trial objectives

The hypothesis to be tested and the objectives of the trial should be clearly stated in the protocol. Clinicians agreeing to take part in a trial should be in a state of **equipoise** regarding the hypothesis to be tested. That is, they should have some uncertainty as to what the outcome will be in what they consider to be the superior treatment or intervention. If a clinician is convinced of the superiority of one of the study treatments it is inappropriate for that clinician to take part in the trial. There should also be reasonable belief that the benefits of the test treatment outweigh its risks and that the treatments are acceptable to both the patients and their physicians.

Treatment schedules

The protocol should give full details of the drugs to be taken together with dose schedules. Expected toxic effects and how to deal with them should be described in detail.

Trial endpoints

The evaluation of a new treatment or practice is made by comparing the outcomes of these interventions between two (or more) similar groups of patients treated at the same time.

The primary and secondary endpoints should be clearly defined in the trial protocol. In a tuberculosis trial the endpoints might be culture conversion rate, relapse rate, time to death, changes in radiographic extent of disease and cavitation, urine tests for compliance, adverse events etc.

One or two endpoints should be assigned as primary. The remaining endpoints will be secondary and only of importance if significant results are found in the primary endpoint(s). In general the study will have its statistical power based on the primary endpoints alone.

In Phase II and Phase III trials, where one of the endpoints is short-term and long-term safety, reporting of serious adverse events, to the Data & Safety Monitoring Committee, should be an immediate and integral part of the protocol.

Impact of trial on quality of care

The impact of a trial should be to improve the quality of patient care both during the trial and after the results have been evaluated.

Patients benefit by participating in a trial because the experimental nature of the trial involves a closer scrutiny of the patients during the trial in order to quickly deal with any adverse event.

At the conclusion of the trial, changes in practice may be introduced which benefit the whole patient population even if they did not participate in the trial.

Investigator's brochure

All investigator's should possess an Investigator's Brochure which is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

VI. STATISTICAL ASPECTS

The null hypothesis

A fundamental issue related to the trial is the **hypothesis**. This may be stated as treatment A is expected be more effective than treatment B. This can never be absolutely proven, only shown to be true with a high degree of probability. **A null hypothesis** of 'no difference' is constructed and the objective of the trial is to demonstrate the likelihood or otherwise that the null hypothesis is true. Thus, the analysis of the trial tests the probability (chance) of the result obtained, under the assumption that the treatments are of equal effect.

The null hypothesis of no difference is rejected if the probability of it being true is less than, or equal to, the level of significance we have chosen; arbitrarily this often the 5% level.

Two types of error are defined:

Type I: the probability of wrongly rejecting the null hypothesis

Type II: the probability of failing to detect a true difference when it exists. The power of an investigation is 1 – Type II error, i.e. a low Type II error corresponds to high power. (Power is often presented as a percentage, not a proportion, hence a type II error of 20% is equivalent to 80% power).

It is necessary to consider what levels of Type I and II error are acceptable. Conventionally the Type I error probability is set at 0.05, a probability rate that predates clinical trials and is attributed to the statistician, R A Fisher, who set it as an arbitrary level in his agricultural field experiments. This is what is known as the **significance level** and a lot of misunderstanding surrounds it. It is popularly believed in some quarters that if a significance level turns out to be 0.06 (or 6%) the study has failed to show evidence of a difference, whereas if it is 0.05 (5%) there is a difference. The distinction between the two levels is minimal. It is important to note that, whereas 1 of 20 versus 5 of 20 is not significant at the 0.05 level (P= 0.18), 0 of 20 versus 5 of 20 is significant (P = 0.05), demonstrating that changing the classification of just one patient can make all the difference!

The type II error rate is usually set at 10 or 20%, that is a power of 90% or 80%. The smaller the type I and type II errors the larger the trial needs to be.

Trial design

The nature of the study needs to be carefully considered. The most common design is a parallel comparison between two groups. Alternatives include factorial designs when two hypotheses are tested within the same trial.

Trials may be designed to show either the superiority of one regimen when compared to another regimen(s), or equivalence of the regimens.

In a **superiority or comparative trial** the null hypothesis is that there is no difference between the treatment arms. In an **equivalence trial**, in contrast, the null hypothesis is that there is a difference between treatments A and B.

What is meant by equivalence? In contrast to superiority or comparative trials the objective of an equivalence trial is to demonstrate equivalent efficacy within predefined limits, say ± 3%. This is known as the confidence interval (CI) and is usually set at 95%.

Equivalence trials are often wrongly understood to be trials that fail to detect a significant difference between two interventions or treatments. Non-significance does not imply no difference, it most commonly occurs because the study has recruited an insufficient number of patients.

In the conduct of an equivalence trial there may not be the same incentive to ensure the trial is conducted to as high a standard as in a comparative trial. Equivalence would mean both treatments are useless, unless we already have evidence to the contrary.

It is very important that an equivalence trial is conducted with the same attention to detail as a comparative trial. Methods and assessments should be the same as for a comparative trial wherever possible. We should expect to find comparable success or failure rates to those in earlier comparative trials.

There are three possible outcomes to the analysis of an equivalence trial:

1) the confidence limit for the difference lies within in the specified range. (The confidence limit is the size of the interval which with a specified probability, say 95%, the true difference lies).

2) the confidence limit lies partly outside the specified range, in that case equivalence cannot be concluded, or

3) the confidence limit lies completely outside the specified range, a rare event!

In a superiority trial there are two possible outcomes:

1) the confidence limit for the difference in effect between the two treatments crosses zero, in which case no significant effect has been demonstrated, or

2) the confidence limit for the difference lies completely to one side of zero, a statistically significant result.

Sample size

After stating the null hypothesis and determining the design of trial the next, and very important, consideration is to determine the size of the trial; in simple terms, how many patients are needed to show an effect? There are several statistical considerations to be made when arriving at this number.

- how small an effect do I want to detect ?
- level of statistical significance, usually P = 0.05 (5%)
- the power (probability of detecting a difference) say P= 0.8 or more (i.e. 80%)
- how many losses to follow-up are expected ?
- how many subjects can I realistically expect to recruit?

Assuming there is a control regimen, there needs to be a realistic assessment of how effective it is, or will be under trial conditions. More difficult is the predicted intervention effect of what may be a new, previously untried, treatment. Here it is essential to be realistic, not overestimating the potential of the treatment effect, and, even if a substantial effect is anticipated, to enrol sufficient numbers to be able to exclude smaller clinically useful effects if the treatment appears to be ineffective.

Power considerations

The protocol should state the power of the study to detect effects and the expected number of non-adherent patients and how they will be handled in the analysis. A plan of analysis needs to be specified.

Power estimates are difficult to be certain about. There is much we do not know, but when planning a trial we need to be realistic in our expectations.

Two other factors which need to be considered are the likely non-adherence rate during treatment and the loss to follow-up after treatment.

Non-adherence is the failure of patients to take their treatment; this dilutes effects of the intervention treatment.

Loss to follow-up reduces the total numbers available for assessment.

Both need to be considered and the effect on the total numbers expected can be dramatic. Even a 10% rate of non-adherence and a further 10% loss to follow-up will increase the size of a trial by more than a third.

Formulae for adjusting power calculations for non-adherence and losses to follow-up are shown below:

- Non-adherence requires an adjustment of $1/(1-d)^2$ to be applied where "d" is the proportion expected to be non-adherent during treatment.
- Losses to follow-up require an adjustment of $1/(1-f)$ where "f" is the proportion expected to be lost to follow-up.

Underpowered trials are a waste of time and resources as they can often fail to detect clinically important differences.

An example of a power calculation (two sided $P = 0.05$ and 80% power) With two different settings shown below:

	(1)	**(2)**
Estimated control response	60%	60%
Estimated intervention response	80%	70%
Expected difference	20%	10%
Total number of subjects		
Assuming no loss to follow-up etc	182	752
With 10% failure to adhere	226	930
With 10% loss to follow-up	204	836
With both 10% drop-out and 10% Loss to follow-up	250	1032

Procedure for randomisation

As has been indicated (**Section III**), this must be done in such a way as to ensure that the future allocations are unknown to the persons enrolling the patients. Bias-free treatment assignment helps to ensure treatment allocation that is free of influence from both the patients and the medical personnel.

How is a randomisation schedule produced? There are several ways it can be done, the simplest being by using tables of random numbers usually found in the back of textbooks of medical statistics. If two groups are to be studied, digits 0-4 can be assigned to one regimen and 5-9 to another. This works well except in the case of a small study, when balance may not be achieved, or when the intake is likely to be slow and it is undesirable to have several successive patients allocated to the same treatment. An extension of the above method is the use of balanced randomised blocks which helps to ensure a balanced allocation throughout the trial. It is important, however, that the size of the blocks is a well kept secret, or is varied, since knowledge of the block size can result in the ability to predict the treatment for the last patient allocated in each block.

A simple randomisation schedule

Use tables of random numbers. For two treatments, A and B; e.g. A : for digits 0-4, B : for digits 5-9, but beware of unbalanced numbers in a small trial. eg 12 on A and 8 on B

Part of random number table:

5	2	7	8	4	3	7	4	1	6	8
9	7	2	4	0	2	3	6	3	1	8
5	9	8	4	3	8	9	5	2	8	4

Randomised blocks of constant size

Use tables of randomised numbers but assign a different sequence of treatments for each digit, eg blocks of four.

AABB for 1, ABAB for 2, ABBA for 3, BBAA for 4, BABA for 5, BAAB for 6 Ignore digits 0,7,8,9

VII. OPERATIONAL ASPECTS

Site requirements

1. **Sites with patients!** It is a very important that the site has an adequate number of suitable patients for the trial. This will immediately rule out some sites that would otherwise appear to be ideal in other respects. However, having an excellent infrastructure and a top quality laboratory is not enough without adequate numbers of eligible patients. The exception may be a site with relatively few patients but good laboratory facilities where detailed sub-studies such a pharmacokinetic studies could be done. It is essential to be realistic about numbers of patients likely to be recruited. A trial that fails to recruit because of unrealistic recruitment goals is a waste of time and money.

2. **A stable population.** For a long term trial it is essential that as many patients as possible can be followed up for the full duration of the study. If half of the patients are lost during follow-up it will be very difficult to interpret the results of such a study. For instance, are such losses more likely to be failures or more likely to be patients who are doing well and don't want to be bothered with regular hospital visits. Large urban centres have both advantages and disadvantages; they may be easier to manage but are likely to have a mobile population, some of whom have only come to the city to get treatment. By excluding them losses to follow-up can be reduced.

3. **Common protocol.** All investigators must agree to follow a common protocol. If they cannot they should not take part in the trial. This does not exclude the possibility that some centres may conduct additional investigations.

4. **Drug supplies.** All the required drugs, in the control and in the intervention arms, must be available throughout the study. It is essential to have a clear plan to ensure continuity of supplies. Procedures need to be in place for the treatment of failures when they occur.

5. **Costs.** Trial site costs should not be underestimated. All costs of a study must be met by the study budget and need to be carefully planned. It would be a

false economy not to budget for items such as extra home visitor support to help with defaulter tracing.

6. **Experienced investigators.** This is an ideal that will not always be possible. If the staff at a proposed site do not have experience in the conduct of trials it will be important for the Central Co-ordinating Bureau to provide training and supervision over and above that which will be given in established sites. In the event of turnover and posting of staff a regular re-assessment of the need for training will be necessary. It would be unwise to enrol large numbers of patients in centres that do not have experienced staff. An alternative, and possibly better, approach to short term training would be to recruit an experienced trial co-ordinator to run the trial and train the local staff on an ongoing basis. Continuity of staff not only improves quality of data but also patient adherence is likely to be better.

7. **Opportunity to input into the trial protocol.** Rather than presenting a final protocol to investigators at the trial sites there should be an opportunity for the local investigators to give their input on the trial design. It may be that the protocol makes impractical demands of the study sites which will need to be re-assessed with a view to modifying the trial design. The greater the sense of involvement and ownership of the trial among the study sites the more likely they are to co-operate with the implementation of the protocol.

8. **Organisational structure.** Sites contributing large numbers of patients to a study should have a local management committee, which will oversee the conduct of the trial in that site. This does not exclude central co-ordination but rather supplements it. Such a committee should have representation from all those involved in the daily running of the trial. In an international trial there may also be an important role for a national committee to whom certain of the main co-ordinating centre's responsibilities can be devolved.

9. **Standardisation**. It is obviously important that all staff who will be involved in the running of the trial on a day to day basis fully understand the protocol and what is required of them. A strong emphasis should be placed on training and where appropriate regular retraining.

10. **Monitoring.** Sites need to be monitored systematically through regular site visits. Regular contacts should also be maintained by post and telephone. It is particularly important to visit a site soon after recruitment has commenced. Other methods of monitoring sites include keeping checks on intake rates, the eligibility of patients being admitted to the study, the time interval between the time patients are seen and the appropriate forms are received in the co-ordinating centre, the proportion of forms with errors or missing data and, if laboratory data are being obtained from a centre, making regular assessments of its quality (see below).

11. **Mycobacteriology laboratory of high quality:** It is essential to have a mycobacteriology laboratory able to perform work to a high standard. Without it the interpretation of the study results becomes almost impossible. In order to monitor the performance of the laboratory there must be regular quality assurance checks including the monitoring of all laboratory output, inclusion of external controls and regular visits by experienced external microbiologists. The role of the local laboratory may be limited to a diagnostic screening facility based on microscopy. When it is intended that culture and susceptibility testing is to be done at an established reference laboratory, there needs to be a reliable way of transporting specimens to that laboratory. For further details see **Section VII** entitled **"Laboratory Aspects".**

12. **Facility for HIV testing and counselling.** In many countries of sub-Saharan Africa the proportion of tuberculosis cases co-infected with HIV is already in excess of 50%; in other countries the proportion is increasing rapidly. There may be a need to know the HIV-status of patients enrolled in trials. This requires having properly trained counsellors available so that those offered testing can be appropriately counselled and followed. In each country, the national laws on testing and disclosure of results have to be taken into consideration.

13. **Computing facilities.** If it is intended to enter data at the trial site, it is important to ensure that the appropriate infrastructure exists. In addition to the availability of the relevant hardware, including voltage surge protectors and uninterrupted power supplies, the staff who will act as data entry officers should be properly trained and be able to handle all of the foreseeable problems which might arise. This includes the need to maintain regular backups and a clear

understanding on how much freedom they have to edit data files. There are advantages to local data management, such as the more immediate identification of missing and problem data if on site data entry is carried out. However, unless the co-ordinating centre has the confidence that it will be done to a high standard, and the quality of the data will not be put at risk, it is better if the study forms are sent to the Central Co-ordinating Bureau for data entry. If forms are faxed there will be little or no delay in handling queries, which can be faxed or emailed back to the individual sites. On site data entry requires careful monitoring.

14. **Good Clinical Practice.** Trials should only ever be undertaken at sites where international standards for patient care (the DOTS strategy) are followed and where programme performance is judged to be good, according to routine assessment carried out by the World Health Organization. Every trial should be carried out under principles governing Good Clinical Practice (GCP). GCP helps to ensure the patient is protected and the data collected are of good quality. For an outline of the principles, see **Appendix I.**

Patient recruitment and follow-up

1. Enrolment criteria

The protocol defines the eligibility and exclusion criteria. These should be as broad as possible so that the results of the trial can be generalised. At the same time consideration should be given to the possibility that the intervention may not be expected to be applicable in some instances, i.e. there may be patients whose type of disease is not expected to respond. In trials of new drugs it may be necessary to exclude those with other serious diseases that may influence the response to treatment. Similarly it is not unusual to exclude patients who are not expected to survive more than a few weeks.

2. Informed Consent

With regard to the rights of the subjects, the protocol must be explicit on the **informed consent procedure.** The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use has published guidelines for the obtaining and documenting of the informed consent procedure[13] The main points are shown in **Appendix II.**

3. Treatment phase

During treatment, it is extremely important that the patients be seen regularly and sufficiently frequently to ensure that any adverse events and non-adherence are dealt with as quickly as possible.

4. Follow up phase

Although the post-treatment phase follow-up visits need not be scheduled as frequently as in the treatment phase, there should, nevertheless, be regular follow-up of a sufficiently long duration that any late effects of the treatment are quickly recognised and dealt with and relapses can be identified and treated.

A detailed schedule of visits required and what investigations will be conducted at each visit should be clearly specified. As well as being part of the protocol this should be apparent within the case record form (CRF) so as to provide a check for the clinician or clinical officer seeing the patient. A computer generated diary can be a useful tool to enable the date of the patient's next appointment to be accurately calculated.

Data management

However large, expensive and sophisticated the trial is in terms of numbers of patients and the data collected, unless careful attention is given to the way the data are captured the whole effort could be wasted. The unambiguous wording of questions is particularly important and this is especially true when forms have to be translated into different languages. After the translation has been done, the translation should be given to a second translator who, without reference to the original, should translate it back again. The back translation should then be carefully compared with the original. Serious discrepancies are not uncommon and if not rectified can render the question useless. It is important to take care to ensure that questions have been phrased in such a way that they will elicit the desired information. Unless the forms have been used before it is advisable to pilot them before the trial begins.

If the form used for data capture can also become part of the patient case record, this will minimise the unnecessary duplication of data to be recorded. Printed laboratory reports can also be used rather than having to transcribe the data to a study form giving opportunity for recording errors. Electronic transfer

of data has obvious advantages. For examples of forms used in a trial, see **Appendix III.** (These forms were prepared by Laura BELTON for use in study C and kindly provided with permission)

Before the advent of the desktop computer, many studies used only individual patient analysis cards. Today few people consider any alternative to the computerised database. However, there are situations where cards can still prove a useful way of data handling. Such a card can be useful in the management of the patient's therapies.

A major advantage of a well-programmed computerised databases is the ability to handle large quantities of data and incorporate range checks and checks for consistency in the data entry process. Range checks include any check for "reasonable" data values, some of which can only be expressed in broad terms such as weight limits and others can be specified exactly. For example, men would not be expected to be pregnant and smear and culture results would take on a limited set of values pre-specified in the bacteriological protocol. Consistency checks compare the latest result with results received earlier; thus a weight gain of 20 kg would not be expected between two consecutive monthly appointments. The checking procedure can be used as a caution, alerting the data entry officer to an odd result. On other occasions it can prevent the result from being entered. Checks such as these may be done at the time of data entry or by running a program subsequent to data entry.

The computer is particularly useful for detecting out of range data, and shifts in laboratory control results and significant variation between observers. A simple analysis of the proportion of forms with errors or missing data can be very useful and in the unlikely, but not unheard of situation when fraud is suspected, the computer may play a valuable role in detecting it.

There are a limited number of packages designed for data collection for clinical trials and there is a need for good generic systems to be developed. Alternatives range from expensive database packages, such as Oracle, to Microsoft Access and spreadsheets like Excel or Lotus. These almost always need to be used in conjunction with a statistical analysis package.

EpiInfo can be used to enter and manage data from clinical trials. The package is free, can be downloaded from the internet[14] and contains within it a simple word processor for creating questionnaires for data entry, an entry module with the ability to program in checks of the type described above in addition to the ability to jump through inapplicable data entry fields. Other modules within

the package include double data entry validation, basic analysis (tabulations etc) and a power calculation module. EpiInfo undoubtedly has its limitations but in a situation when resources are limited it does represent a viable alternative to more sophisticated databases.

The Central Co-ordinating Office

The selection of the co-ordinating centre is of utmost importance. Such a centre will be involved in the development of the protocol, will need to be responsible for implementing the randomisation scheme, and for carrying out a wide range of day to day activities such as collecting, monitoring, entering and checking data and ultimately analysing it. In addition it will need to have:

1. **Expertise**. It needs expertise in biostatistics, epidemiology, computer technology, medicine, administration and data management so as to be able to respond to problems arising day to day.
2. **Impartiality.** There should be no conflict of interest among those employed with respect to the outcome of the trial.
3. **Communications**. There should be good communications with the trial centres, by road, rail or air as well as post, telephone and if possible email.
4. **Monitoring.** Monitoring is the act of overseeing the progress of a clinical trial and of ensuring that it is conducted and recorded in accordance with the protocol, the Standard Operating Procedures, Good Clinical Practice and, where applicable, regulatory requirements.

A monitor, who can be either the principal investigator, trial statistician, or data manager, should make regular site visits to observe the conduct of the trial at each centre. He or she should check on intake rates, the eligibility of patients being enrolled, whether consent is being obtained in a proper way and, among other data collection activities, will pay particular attention to how the endpoint data are being collected. Since too much missing data can make a trial untenable, the monitor should check carefully on data delays and data not received. The monitor's agenda is not to catch out the investigators but to work with them to prevent bad practice, to detect it when it is occurring and to help to instigate appropriate action. In summary, the monitor should be seen as a friendly advisor not an enemy of the investigator.

The rôle of the Central Coordinating Office

The Central Coordinating Office takes the principal rôle in:

1. Overseeing the development of the protocol
2. the recruitment of the participating centres
3. the training of the local staff
4. the despatch of the drugs and study forms to the participating centres
5. randomisation
6. monitoring the conduct of the study
7. data management
8. site visits
9. organising the meetings of the Steering Committee
10. organising the meetings of the Data and Safety Monitoring Committee
11. dissemination of results
12. obtaining funds for each trial

The participating centres

The Principal Investigator at each centre should:

1. participate in the protocol design and development
2. take an active rôle in the coordination and direction of the study
3. train local staff in study procedures
4. oversee all aspects of the study procedure , including patient selection, laboratory investigations and data collection and completion of data forms
5. report immediately to the Central Coordinating Office any serious side effects
6. report promptly any other changes locally which could affect the trial

VIII. ANALYSIS OF DATA

It is important that the protocol clearly sets out the primary and secondary endpoints of the trial. By so doing, any temptation to revise the endpoints to suit the data is removed. It is always tempting to speculate, what if …. ? Such speculation is not out of place, but should be stated for what it is, i.e., a hypothesis-generating exercise, which may result in changes in the design of subsequent studies. Given a data set which shows no difference between two treated groups of patients, it is invariably possible to find at least one sub-group of patients who may, by chance, have benefited from the new treatment.

The protocol should also state at what point, during the trial, interim analyses will be carried out. Interim analyses are important for the detection of unexpected outcomes which could lead to the termination of a trial

Before breaking the code and analysing the data by treatment group, certain procedures must be completed. Outstanding queries, especially those relating to endpoints, must be resolved, and as much as possible of the missing data collected. The data set needs to be checked for errors and omissions, which means performing consistency checks, and entries on the database need to have been verified as correct.

Assessing certain endpoints may be very difficult to do unless totally objective measures such as death from any cause are used. Even double blind studies are rarely 100% blind and it may be necessary to look for ways to obtain assessments not influenced by knowledge or strong suggestions as to what treatment the patient was receiving. Presenting an independent assessor with a summary of the data available for each patient, omitting such information as data on drug side effects, which may unblind the treatment, can do this. Such an assessor needs to have been totally independent of the patient's management throughout the study.

Two schedules of analysis may be considered:

- **Intention to treat (ITT)**
  This method includes ALL the patients according to the regimen they were allocated to irrespective of whether they received the allocated regimen and their subsequent outcome.

- **Per protocol analysis (PPA)**
  This method includes only those patients who were treated according to the protocol.

Analyses per protocol, that is only including those who take all or almost all of their treatment, are inherently biased as they reduce the similarity of the randomised groups by excluding a subgroup of the randomised study patients. Patients who do not take all of the treatment assigned to them in the trial, for whatever reason, are most unlikely to respond in the same way as those who do.

The main analysis should be performed according to intention to treat, that is by the group to which the patient was allocated at randomisation, even if he or she takes an alternative regimen. Only those patients who are ineligible for the study as defined by the inclusion/exclusion criteria of the protocol should be excluded if this can be done without bias. (Some investigators maintain that such patients should remain in the analysis). An acceptable approach would be to analyse the data both ways, reporting the ITT analysis as the one least likely to be biased.

The fact of non-adherence should not, however, be ignored; analyses should include assessments of non-adherence and, if appropriate, its implications.

After the study population has been defined, a comparison of the baseline characteristics will show the extent to which the study groups may differ, particularly in respect of factors that may influence response. The analysis of the primary endpoint should first be conducted without any adjustment for such factors and subsequently including possible factors of prognostic effect as covariates. Only in a comparatively small trial is this adjusted analysis likely to substantially alter findings from the unadjusted analysis.

Subgroup analyses can be informative but should not be used as an excuse for dredging the data in the hope of finding a significant result. Planned subgroup analyses should be identified at the protocol writing stage. In general most secondary and subgroup analyses should be seen as hypothesis generating not as definitive outcomes.

An important consideration is the handling of patients for whom no response outcome is available. Missing responses cannot be assumed to be unrelated to outcome; sometimes patients stop attending because they are well, at other times because they find the treatment unacceptable.

When it comes to the analysis, high levels of non-adherence present problems, but losses to follow-up are even more of a problem. Should they be

regarded as failures of treatment? Poor adherence results in a dilution of effects whereas loss to follow-up results in loss of power and may also disguise inadequate treatment. Patients who stop their treatment are also likely to stop attending for follow-up. Those who cannot be assessed due to default or loss to follow-up are likely to have different outcomes to those completing the trial. Trials should be designed to minimise missing response and every effort should be made to follow-up all randomised patients.

There are several alternative approaches to dealing with patients not available for analysis. These include ignoring all such cases, using all available information and assuming all losses are failures. In the main, these approaches are unsatisfactory, leading to biased outcomes or to an overly conservative conclusion. The use of sensitivity analyses in which different rules are applied to the classification of missing endpoint data allows the reader to make up his own mind and helps to put results into perspective. This approach examines different settings depending on how those with missing data are classified.

After completion of the main analyses, it is often helpful to explore reasons for failure by trying to identify likely prognostic markers. Results of these should however be presented with caution unless certain markers were hypothesised in the protocol to be of predictive value.

When writing up results, particular attention needs to be given to clear statements on the methodology of the trial. Readers need to know just how the patients were managed and the data analysed.

The outcome of the trial must be carefully assessed. Firstly, if a significant difference is obtained, does this always mean that the new treatment is better, or should there be confirmatory trials? Secondly, does a non-significant difference mean no difference, or no demonstrable difference?

IX. LABORATORY ASPECTS

In a multicentre trial, laboratory procedures must not differ to any great extent between the participating laboratories. The main difference will be between the culture medium (Lowenstein-Jensen or Middlebrook) used for culture and susceptibility testing. The following steps should be followed in handling bacteriological specimens:

Specimen collection

Specimens must be collected into dry, sterile sputum collection containers. These containers should be wide-mouthed and have a screw cap with a tight seal. Specimens should always be labelled on the side of the cup rather than on the lid.

Specimen reception

As soon as the specimens are received in the laboratory, they must be recorded in the laboratory register and given an identification number. Whenever possible, specimens should be processed immediately.

Specimen storage

If immediate processing is not possible, they should be stored at 4°C and, if transported to another laboratory, the specimens should be held in a cool box and the transport time should be less than four hours. If the specimens cannot be sent to the laboratory on the same day, they may be stored in a refrigerator for a maximum of five days. They should never be frozen.

Microscopy

This should follow the internationally-recommended procedures.[15] A minimum of 100 fields must be examined before a slide is described as negative.

All smears that are defined as positive by the auramine method must be

over-stained by the Ziehl-Neelsen method to confirm the identity of any fluorescent material.

Decontamination

The decontamination procedure will be determined by the culture medium routinely used.

If Lowenstein-Jensen medium is used, The method of choice, because of its simplicity and low cost, is a modification of the Petroff technique.

1. To a volume of sputum add twice the volume of 4% (w/v) sodium hydroxide (e.g., 2 ml sputum and 4 ml NAOH).
2. Ensure that the container is tightly closed. During the next 15 minutes mix the contents frequently, either by hand or mechanically.
3. Dilute the contents with sterile 0.067M phosphate buffer (pH 6.8) up to the neck of the container. This dilution stops the action of the sodium hydroxide and reduces the specific gravity for centrifugation.
4. Recap the container tightly and mix the contents by inversion several times
5. Centrifuge at 3000xg for 15 - 20 minutes.
6. Pour off all the supernatant fluid into a suitable disinfectant and re-suspend the deposit in the residual fluid that runs back into the container.
7. Inoculate the culture medium.

Culture

The centrifuged deposit should be inoculated onto two Lowenstein-Jensen slopes, one containing glycerol and the second containing pyruvate. Slopes should be incubated at 37°C for not less than 8 weeks. The slopes should inspected weekly.

All suspect colonies should be examined by the Ziehl-Neelsen method to confirm that the colonies are mycobacteria. The identity of the colonies can be further confirmed by inoculating a slope of paraNitrobenzoic acid (pNBA). This should be incubated at 37°C for 10 days. Members of the *M. tuberculosis* complex will not grow on pNBA, will demonstrate cording on ZN staining, and will be non-chromogenic.

Susceptibility tests

Three methods may be used to test drug susceptibility:

- The proportion method
- The resistance ratio method
- The absolute concentration method

One method should be selected to be used throughout the trial at each of the sites. Whatever the method used, assuring the quality of the results is most important. Certain monitoring points are shown below but it is most important for every laboratory to participate in an external proficiency testing programme as an integral part of the quality assurance procedures.

Quality assurance

As part of the quality assurance component of the bacteriological protocol, participating laboratories should record and retain the following information.

1. Equipment performance

- K1 test readings on Class 1 cabinet (alternatively weekly anemometer readings should be recorded and retained).
- Daily incubator temperatures.
- Daily refrigerator temperatures.
- Microscope service record.
- Autoclave temperature records for each run. Alternatively, results of autoclave tape could be recorded.
- Media performance
- Results of growth on Lowenstein-Jensen slopes for each batch.
- Results of inhibition tests on Lowenstein-Jensen slopes for each batch.

2. Laboratory performance

- Laboratory register.
- Smear positivity rate.
- Culture positivity rate.

- Number of smear positive culture negative samples.
- Contamination rate.
- Health and safety
- Ventilation, cleanliness and lighting of laboratory
- Occupational health, incidence of tuberculosis and allergies
- Disposal of infectious materials
- Disinfectants and cleaning
- Accidents and incidents
- Condition of the biological safety cabinet

X. ETHICAL CONSIDERATIONS IN BIOMEDICAL RESEARCH

As a consequence of so called medical experiments carried out on prisoners captured by the Nazi army, during the Second World War, a code of practice, called the Nuremberg Code, was drawn up in 1947 in order to protect human subjects from unethical practices in the name of research. The main conditions were:

- Voluntary consent of subject
- Risks balanced by benefits, minimised
- Scientifically valid research design
- Conducted by qualified scientists
- Subject free to withdraw
- Scientists would terminate experiment if they believed it would result in harm to subjects.

In 1964 these conditions were incorporated, by The World Medical Assembly, in **The Declaration of Helsinki,** which set out stringent guidelines for experiments involving human subjects. The most recent version is shown in **Appendix V.**[16]

Several other international organisations (World Health Organisation (WHO), Council for International Organisations of Medical Sciences (CIOMS)) have published guidelines on research in human subjects which are regularly updated.

Each country must establish its own Ethics Review Committees (ERCs) and, based on international guidelines, draw up its own code on research on their populations. The composition of these committees should reflect expertise on reviewing both the scientific and ethical aspects of each protocol, and represent views other than those of the research community. The ERC should review and approve each protocol prior to its implementation.

In particular, the following points should be addressed :

- Does the study address a priority issue in the community in which it is planned?
- Is the study well designed to optimise the chances of generating knowledge useful to the community in which it is conducted?
- Is the conduct of the study planned in a way that respects the rights of the subjects and minimises the risks to them?
- Does the study allow for informed consent to be obtained from the subjects?
- Is there provision for review and clearance from the relevant institutions?

With regard to the informed consent procedure, see **Appendix II**.

BIBLIOGRAPHY

1 Medical Research Council, Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment for pulmonary tuberculosis. BMJ 1948; ii: 769-782.

2 Dawson J J Y, Devadatta S, Fox W, et al. A 5-year study of patients with pulmonary tuberculosis in a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Bull World Health Organ. 1966; 34: 533-551.

3 East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet 1973; 1: 1331-1339.

4 Hong Kong Tuberculosis Treatment Services/British Medical Research Council. Controlled trial of 6- and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong. Tubercle 1975; 56: 81-96.

5 Singapore Tuberculosis Services/British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1979; 119: 579-585.

6 Lind J. A Treatise of the Scurvy in Three Parts. Containing an inquiry into the Nature, Causes and Cure of that Disease, together with a Critical and Chronological View of what has been published on the subject. London, UK: A Millar, 1753.

7 Abraham E P, Chain E B, Fletcher C M, et al. Further observations on penicillin. Lancet 1941; 2: 177–188.

8 British Medical Research Council Tuberculosis Units, 1946-1986. Studies on the treatment of tuberculosis. Int J Tuberc Lung Dis 1999; 3 (Suppl 2): S231-S279.

9 Dunn D T, Babiker A, Hooker M, Darbyshire J. The dangers of inferring treatment effects from observational data: a case study in HIV infection. Control Clin Trials 2002; 23: 106-110.

10 Fischl M A, Richman D D, Grieco M H, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987; 317: 185-191.

11 Quigley M A, Mwinga A, Hosp M, et al. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. AIDS 2001; 15: 215-222.

12 International Union Against Tuberculosis and Lung Disease. Research methods for promotion of lung health. A guide to protocol development for low-income countries. Paris, France: IUATLD, 2001.

13 International conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guidelines. Guideline for good clinical practice, E6. Geneva, Switzerland: ICH, 1996. www.ich.org

14 Centers for Disease Control and Prevention. Epi Info. www.cdc.gov/epiinfo/ Accessed August 2004.

15 International Union Against Tuberculosis and Lung Disease. Technical Guide. Sputum examination for tuberculosis by direct microscopy in low-income countries. Paris, France: IUATLD, 2000.

16 World Medical Association. Policy. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Ferney-Voltaire, France: WMA, 2002. www.wma.net/e/policy/b3.htm Accessed August 2004.

17 Medical Research Council. MRC guidelines for good clinical practice in clinical trials. London, UK: MRC, 1998. www.mrc.ac.uk/pdf-ctg.pdf Accessed August 2004.

APPENDIX I

Good Clinical Practice

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use[13] has defined Good Clinical Practice (GCP) as an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible.

The principles of GCP are:

1. Clinical trials should be conducted in accordancewith the ethical principles that have their origin in the Declaration of Helsinki.
2. The foreseeable risks should be weighed against the anticipated benefit both to the patient and the community.
3. The rights, safety and well-being of the trial subjects prevail over the interests of science and society.
4. Freely given informed consent should be obtained from every trial subject before their participation in the trial.
5. Trials should be scientifically sound and described in a clear detailed protocol.
6. The protocol must have received the approval of an Ethics Review Committee.
7. The medical care given to, and medical decisions made on behalf of, trial subjects should always be the responsibility of a qualified physician.
8. The Principal Investigator and each individual involved in conducting the trial should be qualified by education, training and experience to perform their respective tasks.
9. The confidentiality of records that could identify a trial subject should be protected.

10. All trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. Investigational products should be manufactured, handled and stored in accordance with Good Manufacturing Practice
12. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed trial.
13. Systems for quality assurance of every aspect of the trial should be established.

Another source of guidelines on GCP is the publication of the Medical Research Council entitled MRC guidelines for good clinical practice in clinical trials[17]

APPENDIX II

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for the obtaining and documenting of the informed consent procedure

1. Prior to the beginning of the trial, the investigator should have the Institutional Review Board / Institutional Ethics Committee's written approval.
2. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
3. The consent form, should not contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights,
4. If the subject is unable to provide informed consent, the subject's legally acceptable representative, should be fully informed of all pertinent aspects of the trial.
5. The language used information about the trial should be as non-technical as possible.
6. Ample time and opportunity should be given to inquire about details of the trial and to decide whether or not to participate in the trial.
7. The written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.
8. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.
9. Any information to be provided to subjects should include explanations of the following:
    (a) That the trial involves research.
    (b) The purpose of the trial.
    (c) The trial treatment(s) and the probability for random assignment to each treatment.
    (d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.
(f) Those aspects of the trial that are experimental.
(g) The reasonably foreseeable risks or inconveniences to the subject and the reasonably expected benefits.
(h) The compensation and/or treatment available to the subject in the event of trial-related injury.
(i) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(j) That records identifying the subject will be kept confidential. If the results of the trial are published, the subject's identity will remain confidential.
(k) The expected duration of the subject's participation in the trial.
(l) The approximate number of subjects involved in the trial.

APPENDIX III

Examples of trial forms

Patient Content

Patient's Full Name:

Please use first letter of each name to record patient's initials below and on subsequent forms.

Study Number:	**Patient's Initials:**	**Centre:**	**Date (dd/mm/yy):**
☐☐☐☐			☐☐/☐☐/☐☐

PATIENT CONSENT

I _____have been told by Dr. _____ that I have pulmonary tuberculosis which can be cured if I take my medicines as directed.

I have been invited to participate in a trial in which the drug formulations will be different from those of the standard regimen, but the results of which are expected to be as effective if I take my medicines as directed.

I understand that I will be tested for HIV infection but the result will be kept confidential and I will only be told the result if I wish to know it.

Dr. _____ has explained the nature of the project to me and the commitment it will require of me for the next thirty months.

I have understood all that has been explained to me in the Patient Information Sheet and agree to participate in the trial.

Signature of patient: _____ Date (dd/mm/yy): ☐☐/☐☐/☐☐

Date (dd/mm/yy):	**Name:**	**Signature:**
☐☐/☐☐/☐☐		

Patient's Home Details

Patient's Full Name:

Please use first letter of each name to record patient's initials below and on subsequent forms.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):
☐☐☐☐			☐☐/☐☐/☐☐

PERMANENT ADDRESS

1) **Permanent address:** _____

_____

2) **Telephone number(s):** _____

3) **Duration of residence at permanent address:** **Years** ☐☐ **Months** ☐☐

4) **Distance from hospital (km):** ☐☐

5) **Date of home visit:** ☐☐/☐☐/☐☐

PRESENT ADDRESS (if different from above)

1) **Present address:** _____

_____

2) **Telephone number(s):** _____

3) **Duration of residence at present address:** **Years** ☐☐ **Months** ☐☐

4) **Distance from hospital (km):** ☐☐

EMPLOYMENT

1) **Occupation:** _____

2) **Name and address of employer:** _____

_____

3) **Telephone number(s) of employer:** _____

4) **Duration of present employment:** **Years** ☐☐ **Months** ☐☐

DETAILS OF CLOSE RELATIVE

1) **Name and address :** _____

_____

2) **Telephone number:** _____

3) **Relationship:** _____

DETAILS OF ADDITIONAL CLOSE RELATIVE

1) **Name and address :** _____

_____

2) **Telephone number:** _____

3) **Relationship:** _____

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

Pretreatment Report

This form should be completed for month 0 only. Please complete in capital letters.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):
☐☐☐☐			☐☐/☐☐/☐☐

Date of Birth (dd/mm/yy):	Age (years):	Sex (M/F):	Weight (kg):	Height (cm):
☐☐/☐☐/☐☐	☐☐	☐	☐☐☐	☐☐☐

INCLUSION CRITERIA	Yes	No
A. Two sputum specimens positive for tubercle bacilli on direct smear microscopy	☐	☐
B. Either no previous anti-TB chemotherapy, or less than one month (4 weeks) of previous chemotherapy	☐	☐
C. Aged 18 years and over	☐	☐
D. A firm home address that is readily accessible for visiting	☐	☐
E. Agreement to participate in the study and to give a sample of blood for HIV testing	☐	☐

EXCLUSION CRITERIA	**Yes**	**No**
A. Patient in a moribund state	☐	☐
B. Has TB meningitis	☐	☐
C. Presence of any of the pre-existing non-TB diseases outlined in the protocol	☐	☐
D. Known to be pregnant, or breast feeding	☐	☐
E. Presence of a psychiatric illness or alcoholism	☐	☐
F. Has contraindications to any medications in the study regimens	☐	☐

Patient is ineligible for the study if any of the shaded boxes have been ticked

ALLOCATED REGIMEN

1) Please identify allocated regimen: 1 ☐ or 2 ☐ Go to Q2

SPUTUM SPECIMENS *(please also complete form 3a)*

2) Please collect two sputum specimens and record dates (dd/mm/yy) collected below:

Specimen A: ☐☐/☐☐/☐☐ Specimen B: ☐☐/☐☐/☐☐ Go to Q3

SMOKING

3) Has the patient ever smoked cigarettes? **NO** ☐ **Go to Q4** **YES** ☐ **Give details:**

Does the patient smoke now? **NO** ☐ Go to Q4 **YES** ☐ Go to Q4

URINE GLUCOSE

4) Please record results of urine glucose test: (tick one only) **Present** ☐ **Absent** ☐ **Not Done** ☐ **Go to Q5**

CHEST RADIOGRAPH

5) Was chest radiograph done? **NO** ☐ **End form** **YES** ☐ **Give details:**

a) Date of chest radiograph (dd/mm/yy): ☐☐/☐☐/☐☐

b) Was there bilateral disease? NO ☐ YES ☐

c) Were cavities present? NO ☐ YES ☐ End form

Date (dd/mm/yy):	**Name:**	**Signature:**
☐☐/☐☐/☐☐		

Progress Report

This form should be completed at months 1, 2, 3, 4, 5 and 6. Please complete in capital letters.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):	Month:
☐☐☐☐			☐☐/☐☐/☐☐	☐☐

INTERRUPTION OF TREATMENT DUE TO DRUG INTOLERANCE

1) Has patient had any symptoms or signs of drug intolerance since the last progress report?

NO ☐ Go to Q3 **YES** ☐ Give details:

Details of side effects due to drug intolerance: (please see side effects list in SOPs for Completion of Study Forms) Go to Q2

2) Has treatment been interrupted due to side effects?

NO ☐ Go to Q3 **YES** ☐ Give details:

a) Date of interruption of treatment due to drug intolerance: ☐☐/☐☐/☐☐

b) Suspected drugs: (Tick all that apply) E ☐ H ☐ R ☐ Z ☐ Go to Q3

c) Has treatment been changed? NO ☐ Go to Q3 YES ☐ Please give details: Go to Q3

OTHER INTERRUPTIONS OF TREATMENT

3) Has the patient had any other interruptions of treatment since last progress report?

NO ☐ Go to Q4 **YES** ☐ Give details:

a) Reasons for interruption of treatment: (please see other interruptions list in SOPs for Completion of Study Forms)

b) Number of days treatment missed as result of interruption of treatment: Go to Q4

Note: If number of days treatment missed is > 7, complete interruption of treatment section on form 4.

FAILURE (months 5 & 6 ONLY)

4) Is the patient to be retreated as result of failure?

NO ☐ Go to Q5 **YES** ☐ Give details:

a) Date start of retreatment (dd/mm/yy): ☐☐/☐☐/☐☐

b) Reasons for retreatment: (tick all that apply) Clinical ☐ Bacteriological ☐ Radiological ☐ Go to Q5

Comments (if any)

SPUTUM SPECIMEN (months 2, 3, 5 & 6 ONLY) (please also complete form 3a)

5) Please collect sputum specimen and record date (dd/mm/yy) collected below:

Specimen A: ☐☐/☐☐/☐☐ Go to Q6

TABLETS PRESCRIBED FOR NEXT MONTH

6) Please record number of tablets prescribed for next month:

EHRZ ☐☐☐ E ☐☐☐ H ☐☐☐ R ☐☐☐ Z ☐☐☐ RH ☐☐☐ End form

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

Laboratory Request / Report

This form should be completed for months 0, 2, 3, 5, 6, 8, 10, 12, 15, 18, 24, 30 or for any additional months.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):	Month:
☐☐☐☐			☐☐/☐☐/☐☐	☐☐

SPUTUM SPECIMEN(S) (To be completed by Treatment Supervisor)

1) Please tick purpose of specimen: (tick one box only)

Routine collection for month 0 (Form 0): ☐ (collect 2 samples)

Routine collection for months 2, 3, 5, 6, 8, 10, 12, 15, 18, 24, 30 (Form 2 or Form 5): ☐ (collect 1 sample)

Patient is to be retreated: ☐ (collect 2 samples)

Additional specimens collected: ☐ (collect 2 samples)

2) Please complete date(s) (dd/mm/yy) specimen(s) collected below:

Specimen A: ☐☐/☐☐/☐☐ Specimen B: ☐☐/☐☐/☐☐ Go to Q3

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

SMEAR RESULT(S) *(To be completed by Laboratory Technician)*

3) Please complete smear results for specimens below:

Smear Result A: Lab Number: _____ Smear Result: ☐☐

Smear Result B: Lab Number: _____ Smear Result: ☐☐ (if applicable)

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

CULTURE RESULT(S) *(To be completed by Laboratory Technician)*

4) Please complete culture results for specimens below:

Culture Result A: Lab Number: _____ Culture Result: ☐☐

Culture Result B: Lab Number: _____ Culture Result: ☐☐ (if applicable)

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

Interruption of Treatment, Default, Death

This form only needs to be completed if the patient either has an interruption of treatment >7 days, defaults or dies.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):
☐☐☐☐			☐☐/☐☐/☐☐

INTERRUPTION OF TREATMENT > 7 DAYS

1) Date patient last attended treatment clinic (dd/mm/yy) ☐☐/☐☐/☐☐ **Go to Q2**

2) Has the patient's home been visited? **NO** ☐ **Go to Q4** **YES** ☐ **Give details:**

a) Date(s) patient's home visited (dd/mm/yy): ☐☐/☐☐/☐☐ ☐☐/☐☐/☐☐

b) Was patient seen? **NO** ☐ Go to Q2c **YES** ☐ Go to Q3

c) Was relative seen? **NO** ☐ Go to Q3 **YES** ☐ Go to Q3

3) If the patient was away, expected date of return (dd/mm/yy) ☐☐/☐☐/☐☐ **Go to Q4**

4) Has patient returned to treatment? **NO** ☐ End Form **YES** ☐ Give details:

Date of return to treatment: ☐☐/☐☐/☐☐ End form

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

DEFAULT

1) Date patient last attended treatment clinic (dd/mm/yy) ☐☐/☐☐/☐☐ **Go to Q2**

2) Has the patient's home been visited? **NO** ☐ Go to Q4 **YES** ☐ Give details:

a) Date(s) patient's home visited (dd/mm/yy): ☐☐/☐☐/☐☐ ☐☐/☐☐/☐☐

b) Was patient seen? NO ☐ Go to Q2c YES ☐ Go to Q3

c) Was relative seen? NO ☐ Go to Q3 YES ☐ Go to Q3

3) If the patient was away, expected date of return (dd/mm/yy) ☐☐/☐☐/☐☐ **End form**

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

DEATH

1) Date of death (dd/mm/yy): ☐☐/☐☐/☐☐ Go to Q2

2) Place of death: Hospital ☐ Home ☐ Other ☐ Go to Q3

3) Informant: Relative ☐ Neighbour ☐ Other ☐ Go to Q4

4) Cause of death: End Form

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

Follow-up Report

This form should be completed for months 8, 10, 12, 15, 18, 24, 30 or when relapse is suspected.

Study Number:	Patient's Initials:	Centre:	Date (dd/mm/yy):
☐☐☐☐			☐☐/☐☐/☐☐

RELAPSE

1) Has the patient had symptoms or signs of relapse since the end of the allocated regimen?

NO ☐ Go to Q2 **YES** ☐

Reasons for relapse: (tick all that apply)

Clinical ☐ Bacteriological ☐ Radiological ☐ Go to Q5

Comments (if any)

RETREATMENT

2) Has the patient received any antituberculosis treatment since the end of the allocated regimen?

NO ☐ Go to Q3 **YES** ☐ Give details:-

Date of start of retreatment (dd/mm/yy): ☐☐/☐☐/☐☐

SPUTUM SPECIMEN(S) *(please also complete form 3a)*

3) Please collect one sputum specimen and record date (dd/mm/yy) collected below:

Specimen A: ☐☐/☐☐/☐☐

4) Please collect second specimen if patient has symptoms or signs of relapse:

Specimen B: ☐☐/☐☐/☐☐ End form

Date (dd/mm/yy):	Name:	Signature:
☐☐/☐☐/☐☐		

APPENDIX IV

Terms of reference for trial committees

The Ethics Review Committee

Establish requirements for research involving human subjects.

Review the final version of protocols and either approve, require modifications of, or disapprove them, based on their compliance with established requirements of:

- voluntary, informed consent procedure.
- risk-benefit assessment with minimization of risks
- fair selection of subjects
- review the frequency of unexpected serious and fatal adverse events
- relevance of trial to community
- availability of benefits to community
- ownership of trial results

Once the protocol has been approved by the ERC, the monitoring of the progress of the trial would be taken over by the DSMC and the protocol would only be resubmitted to the ERC **only** in the case of a major amendment requiring the modification of the Patient Information Sheet (PIS) and of the consent form.

The Steering Committee

1. To review at least annually the work of the trial centre, including progress in current studies and plans for new trials.
2. To ensure that the work of the trial centre is consistent with internationally established guidelines on good clinical practice and that ethical considerations, including appropriate ethical review of studies involving human subjects and informed consent of study participants, are applied to all studies.
3. To make recommendations on needed clinical trials which might be undertaken by the trial centre.

4. To assist in the identification and recruitment of clinical trials sites.
5. To assist the trial centre in ensuring that adequate financial support is available for the trial activities.

The Data and Safety Monitoring Committee

1. To review safety data every six to twelve months, in particular all serious adverse events possibly attributable to the trial drugs, such as local reactions or unexpected deaths. These data will be provided as blinded data. However, should any member of the committee express any concern regarding the data, the data may be unblinded.
2. To monitor the conduct of the trial with respect to the ethical aspects of the trial.
3. To reevaluate projects at intervals appropriate to the degree of risk, but not less than annually

12. To monitor serious side-effects**, Particularly in Phase II and Phase III trials where short- term and long-term safety of the interventions are a primary endpoint,** nature of event, impact on participants, what corrective measures taken

5. To make sure that research results are published (otherwise unnecessary risk for participants if data are not used)
6. To assess the results of the formal interim analysis with the possibility of advising the Steering Committee that the trial should be modified or discontinued.

   The formal interim analysis will be undertaken after half of the patients have been followed for twelve months since randomisation. No formal stopping rule will be set. However, the DSMC will advise the chairman of the Steering Committee that the trial should be stopped if, in their view, the randomised comparison in the trial has provided both:

   a) proof beyond reasonable doubt that for all, or for some, types of patients the trial treatment is clearly contraindicated in terms of a net difference in relapse rates and mortality, and
   b) evidence that might reasonably be expected to influence the patient management of clinicians aware of the results of any other studies.

The DSMC may initiate an interim analysis if there is concern about the number of adverse events possibly attributable to the drugs.

APPENDIX V

The Declaration of Helsinki

World Medical Association Declaration of Helsinki[16]

Ethical Principles for Medical Research Involving Human Subjects.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the;

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people.
   The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for all Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/ mental condition that prevents obtaining informed consent is a necessary

characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of

research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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