

Randomised Controlled Trials (RCTs) – Essentials

Y H Chan



The prospective, randomised, controlled, blinded (if possible), sample-size calculated study with a pre-planned statistical analysis and trial monitoring is undoubtedly the gold standard for a therapeutic or interventional clinical study.

RCTs carried out recently have discredited some treatments deemed effective by observational studies include (to mention a couple), hormone replacement therapy to prevent coronary heart disease events⁽¹⁾ and arthroscopic surgery for osteoarthritis of the knee⁽²⁾.

The top-down research process in the conduct of an RCT could be broadly categorised into three stages (see Table I).

Each stage of the process must be carefully planned and carried out. A poorly designed, poorly conducted and poorly reported trial is a violation to the rights of the subjects who gave consent to participate in a study; this is not ethical (ICH E6, Guidelines on Good Clinical Practice⁽³⁾). Thus it is not only the sole responsibility of the principal investigator of the trial but all the researchers/collaborators (including patients!) involved in the trial to make sure all the stages are being carried out with the highest standards.

The main objective of a clinical trial is to determine the differences (if any) between groups in outcomes of interest. However, these differences could be due to bias (imbalances between groups unrelated to treatment but related to outcome) or to chance alone (random error). In this article, we shall discuss the techniques (in general, for each stage of the research process) to limit the error of wrongly detecting a non-existent difference.

STAGE 1: STUDY DESIGN

Setting up the protocol

The protocol is essentially the 'bible' for the conduct of the study concerned. The background and the rationale for conducting the study should be given. The objective(s) of the study should be clearly stated and the appropriate design chosen to provide the desired information. Here documentation on how the study is to be conducted, for example, details of subject treatment with stated dosage regimens,

treatment schedules and frequency of follow-ups must be specified.

Primary and secondary variables

Every study must have a primary objective and usually several secondary variables. These variables must be carefully selected and defined to address the corresponding objectives of the study in order to enhance the reliability and validity of the eventual findings.

The primary variable must be capable of providing the most clinically relevant evidence related to the aim of the study and should reflect the accepted norms and standards in the relevant field of research. This variable will be used in the sample size calculations and also for primary data analysis that will lead to the trial reporting.

Frequently, there is more than one clinical endpoint of interest. In such a situation one needs to be cautious of multiplicity concerns which will result in an increased error of detecting a false difference by chance. Also if multiple primary variables arrive at inconsistent results, interpretation becomes difficult. (This issue of multiplicity will be addressed in a future article).

The protocol should define the importance and effect of the secondary variables in the interpretation of the study results. Secondary variables arise as relation to the primary outcome (subgroup analysis) or as measurements of effects related to the secondary

Table I

Stage 1. Design of study

Setting up the protocol
Defining primary and secondary outcomes
Study population, inclusion and exclusion criteria
Sample size and statistical plan
Design of Case record forms
Logistical issues for conduct

Stage 2. Conduct of study

Monitoring of the study
Data capture, database design and data entry

Stage 3. Statistical analysis & reporting

Clinical Trials and
Epidemiology
Research Unit
226 Outram Road
Blk A #02-02
Singapore 169039

Y H Chan, PhD
Head of Biostatistics

Correspondence to:
Y H Chan
Tel: (65) 6317 2121
Fax: (65) 6317 2122
Email: chanyh@
cteru.gov.sg

objectives which may be useful in exploratory investigations to generate future study hypothesis. The issue of multiplicity is also needed to be considered here.

Study population

The broad aim of the clinical research investigation is to show that the treatments concerned are safe and efficacious, to the extent that the risk-benefit ratio between the active and control treatments is favourable and acceptable. Thus the particular subjects who may benefit (the inclusion and exclusion eligibility criteria checklists) should be clearly defined in the protocol development process.

The principles and practices concerning the protection of trial subjects are stated in the ICH Guideline on Good Clinical Practice (ICH E6).

Sample size and statistical plan

To limit the chance of a difference between treatments happening, a large enough sample must be recruited. In any sense, the sample size should be relevant to detecting a clinical significance first and then a statistical significance. For instance, we are able to find a statistical significance of a 1 mm Hg drop in blood pressure between two treatment medications for hypertension with a huge sample size but clinically this difference is not relevant.

One of the many reasons to know the number of subjects required is to calculate the budget for the study. More importantly, the researcher (and grant awarding bodies) must be reassured that the money will be well spent on a high likelihood of the study giving unequivocal results. Gore & Altman (1982)⁽⁴⁾ illustrated that the number of subjects recruited in a study is itself an ethical issue.

Besides having a good documentation in the protocol on how the sample size was derived, it is also essential that a statistical plan should be included. This plan should provide the statistical analysis to be performed for the primary and secondary variables. This will curb the risk of data dredging leading to distorted reporting, with a post hoc emphasis on the most statistically impressive findings.

Case record forms (CRFs)

The main function of the CRFs is to collect the data needed to answer the trial's objectives. Though electronic means of data-capturing are available, transcribing data from source documents (patients' medical records) onto CRFs is commonly used. The data collection questions on the CRF must not be ambiguous and be consistent with the protocol. For easy and efficient filling in, the flow of entry on

these forms should be in accordance to the treatment schedule set out in the protocol. It is recommended that these forms be printed with tick boxes for multiple choice questions and boxes for recording of laboratory and other data. Instructions on how each question is to be filled must be given.

Proper codings should be kept consistent throughout the form; this will aid the data-entry process.

Logistical issues for conduct

It is one thing to have a properly designed study and another to have a properly conducted study. It is essential that before a trial begins, all logistic issues must be ironed out. Who is going to take consent, do the necessary tests, collect data and so on, must be spelt out within the clinical department. A good procedure to call back subjects for follow-up must be devised. A study with lots of missing data is as good as one with no data. *No data no results*. An investigator could be very engrossed in seeing the trial's subjects but with no data collected; no valid results will be produced; this is a waste of time and again not ethical.

STAGE 2: STUDY CONDUCT

Randomisation

Randomisation, whereby different treatments are allocated to patients in a trial by a chance mechanism, eliminates selection bias and balance prognostic factors to create a control group as similar to the treatment group in all respects (both known and unknown factors).

It is essential that the clinician should not be able to guess or know the next available treatment to be allocated for the patient. This avoids the possibility of subconscious or conscious interference in the allocation process based on preconceived preferences about the merits of the different treatment options. Thus, alternate assignment of treatment, sequential numbering (date of birth, alternate day allocation, odd even identification numbers), shuffled method (putting treatments in a bag and picked) must be avoided.

Typical methods for issuing random allocations are the use of sealed envelopes (the randomisation code list, prepared by a biostatistician, must not be given to the randomising investigator), telephone or web randomisation (both techniques are usually maintained by a Clinical Trials Unit).

Blinding (Masking)

During the course of an open-label trial (where both clinicians and patients know what intervention is given), perceptions about the advantages of one

treatment over another can influence assessments of outcomes. To control for such bias, blinding (if possible) is performed. This means the successful masking of treatment allocation, with 'matching' active and placebo.

In a single blind design, because the patients are usually not aware of the allocated treatment, bias in reporting of symptoms or events will be controlled. The double blind design, where neither clinician nor patient knows which treatment is given, has the advantage of controlling both reporting and assessment bias. In this case, emergency unblinding procedures must be always promptly available.

For double blind studies, a proper procedure for packaging of the matching placebos and actives, according to the randomisation codes, must be drawn up by the packaging company and this should be witnessed by the sponsor or the independent monitor. If more than one bottle of medications is to be given at various times, the trial/nurse co-ordinator despatching the medications must keep an accurate account.

Monitoring

"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice (GCP), and applicable regulatory requirements" (ICH E6, 1996). The purpose is to safeguard and enhance the quality of the data which leads to the validity of the results reported.

The monitoring could be carried out by an appointed person in the researcher's team but it is recommended that a monitor from a Clinical Trials Centre be engaged for independence or conflict of interest. Issues to be monitored include patient accrual rate, protocol compliance, adverse events/toxicity and data quality.

At times actual accrual does not correspond to projected accrual rate which will affect the duration for study completion. The root of the problem needs to be arrested: possible areas to look into are perhaps the eligibility criteria which need to be revised or the consent process too complex for patients or including more participating centres.

Protocol compliance and adverse events/toxicity monitoring are essential to be monitored for validity and safety reasons respectively. CRFs should be carefully checked for missing data and inconsistencies. Any change made on the form must be initialled and dated without erasing the original entry and with reasons annotated. These checks should be carried out on a periodically planned basis depending

on the type of data. For example, data for specific-scheduled blood tests not done may not be available anymore. Source data verification should be carried out.

Database design and data capture

A proper database should be used for the entering of data from the CRFs. Most commonly used software for data capturing currently are EXCEL, ACCESS and SPSS. Excel and ACCESS are easily available on most personal computer but SPSS, usually an institution's acquired software, may not be easily available and would be rather costly to be owned personally. The above packages though could be used for maintaining a database (medium sized studies) but do not have the capability of facilitating an audit trail to keep track of data modifications and tracking of patients' follow-up status.

CLINTRIAL (<http://www.phaseforward.com>) and ORACLE CLINICAL (<http://www.oracle.com>) are two widely used systems that not only provide an audit trail facility but also have security setups for using the different modules (design of database, data entry, data retrieval, data modifications, etc). Standard code lists and dictionaries (e.g. MEDDRA) could be put in place especially for multi-centre studies. Validation and derivation rules for data quality, data integrity and customised reporting of discrepancies are also available.

Under ICH E6, section 5.5.3, some essential requirements for an electronic system for data handling include the provision that the system permits data changes but with documentations (an audit trail), maintain adequate backup of the data and a security that prevents unauthorised access to the data.

STAGE 3: STATISTICAL ANALYSIS AND REPORTING

The final report translates the clinical research carried out into a document which should present the important findings to the reading audience. This report should cover the entire process of the development of the protocol to the statistical analysis.

It should provide details on ethical approval and participants' consent to the study. The design of the study and how the study was carried out with the patients' demographics should be described. The treatments administered, procedure for blinding (if available) and randomisation outlined. The primary/secondary endpoints clearly defined, with the planned sample size stated and document the statistical tests to be carried out with an assurance of data quality. ICH E3: Structure and Content of Clinical Study Reports gives a detailed discussion on this subject.

Additionally, several major journals have adopted the CONSORT guidelines⁽⁵⁾ for publication of clinical trials to enhance the standards of both statistical and scientific reporting.

CONCLUSIONS

It is not possible to fully document all the important aspects of clinical trial conduct here. The reader is encouraged to do further reading. The general considerations for clinical trials are discussed in the ICH guideline E8 General Considerations for Clinical Trials (ICH, 1996).

The ICH E6: GCP - Guideline for Good Clinical Practice outlines the activities of the investigator, the sponsor and the monitor from the planning stages to the final report, to ensure the data and the reported results are both credible, accurate and useful. ICH E9: Statistical Principles for Clinical Trials would be applicable for biostatisticians.

Fig. 1 shows the percentage of contribution for each stage of the research process to the success (validity and reliability of the results) of a clinical study. At least 50% comes from the conduct and data collection stage (the garbage-in garbage-out principle) and with the design stage (correct design configuration to answer the aims of the study) properly set up, there's no fear of not getting the right biostatistician to complete the analysis.

Beginners to RCTs are recommended to refer to Pocock (1983)⁽⁶⁾ and Piantadosi (1997)⁽⁷⁾ for a good foundation, and to seek help for relevant advice before embarking on a clinical study.

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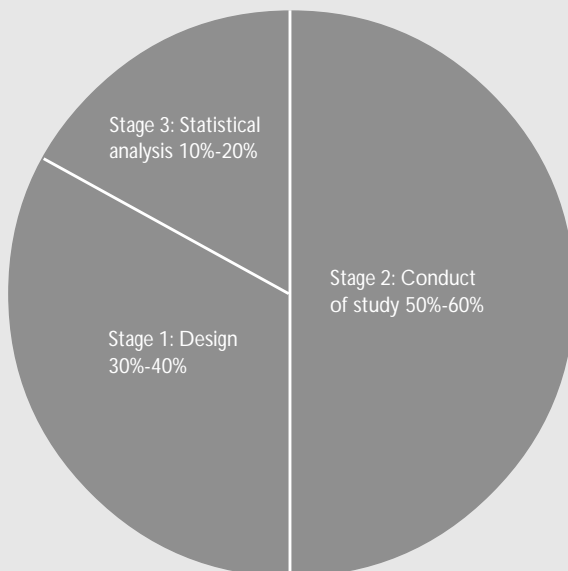


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