Operational aspects of a clinical trial

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Declaration of interest *

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Activities for a company in relation to a particular product / product group	NO	Currently or last year	Over a year ago but less than 5 years ago	More than 5 years ago
Employee	X			
Adviser	X			
Principal researcher	X			
Member of steering committee, an advisory committee or similar organization	X			
Researcher (not principle) for the development of product	X			
Financial interest in pharmaceutical company	X			
Patent on a product	X			
The organization in which I work has a repayment or other funds from pharmaceutical companies (I will not receive individual earnings)	X			

ut declaration of interest of members of scientific committee and

The planning and development of a Clinical study requires the interaction of many professionals who during the course of the research will use many reference documents.

During the progress of the study, a fundamental role is played by the Coordination Committee (especially in large multi-centre studies) which acts as a continual centre of communication between all the structures involved in the experimental study and which can make decisions regarding, for example, amendments to the protocol or suggest the premature closure of the study.

This last decision however is generally taken by the unit defined as the DSMC (Data Safety Management Committee) made up of people who are independent from the study with expertise in both medicine and statistics; this group therefore has the job of periodically evaluating the progress of the study and takes decisions related to its continuation or suspension.

Other people or groups may also be involved in the revision of the endpoint, in the management of the data and in communication with the patients.
Another very important role is in monitoring, performed by a specific person – the Monitor – whose job within the study is to assume the fundamental role of controlling the "regulatory" quality of the running of the study and the quality of the data collected.

The evaluation of the safety of the use of the medicine is also a fundamental aspect of clinical experimentation and assumes a different role in the various phases of development of a new product. A good protocol should indicate specific guidelines or diagnostic or therapeutic algorithms for the management of adverse events, both as a guarantee for the patients and to give the advantage of uniform event management during the analysis.

All the activities of clinical experimentation are subject to intense verification, both by the personnel of the sponsor and by national or international regulatory authorities; these controls are generally of two types: due to specific problems or undertaken as routine controls.

The quality of a clinical trial involves various parameters – it is “multidimensional”. A successful trial should be well designed, well conducted, and well analyzed, giving reliably interpretable results that can be put to good use. Some of these features fall under the heading of internal validity (meaning the appropriateness, coherence and robustness of the methods); others regard external validity – the relevance of the endpoints and the results to everyday clinical practice.

The conceptual core of a trial is its design, but the strength of its conclusions also depend on how it was conducted. It is therefore essential to focus clearly on this when planning and running the trial.

A meticulously designed trial with impeccable methods may even risk failure if it suffers organizations defects – such as not obtaining full follow-up information, or appropriate instrumental data, or carefully collected biological samples. When it comes to writing up the results defects like this will show through, and how the reader – or a referee – is convinced of the trial's conclusions will depend on these factors.

Reference documents

- Full background documentation must be provided for all the centers and structures involved in the trial. This means general regulatory references and specific documentation pertinent to the trial.

Reference documents
Good clinical practice (GCP) and other regulatory refereces
The study protocol
Operating procedures

Good Clinical Practice: general content

Good Clinical Practice: general content
Terminology
General principles
Definition and tasks of the ethics or institutional commitee
Definition and tasks of the investigator
Definition and tasks of the sponsor (or promoter)
Protocol
Investigator’s brochure
Essential papers for conducting a clinical trial

Key figures according to Good Clinical Practice

Key figures according to Good Clinical Practice
The ethics or institutional committee
The investigator
The sponsor (or promoter)
The pharmacist
The patient

Documentation according to Good Clinical Practice

Documentation according to Good Clinical Practice
Description of the document
Purpose of the document
When prepared and used
Archiviation by the investigator
Archiviation by the sponsor

The protocol and operating procedures serve as the specific reference for the trial and are the documents most consulted during it. The protocol itself merits a whole book and it is difficult just to summarize its contents.
The protocol designer has to combine and balance many details: experimental rigor, topicality of the clinical question, frequency, invasiveness, acceptability and feasibility of the procedures required, representativeness of the sample, the need to obtain clinical information in reasonable time but also to ensure it is solid and transferable, ethics and criteria for experimental methods, reasonableness in conduction and respect of the original question.

The protocol has to be acceptable to patients, to the ethics committee, pharmacists, nurses, doctors, statisticians, monitors, laboratory and administrative staff.
It must be compatible with patients' schedules and with the clinical center's work, and every effort must be made to foresee anything that might happen during the trial.

In practice, it involves transferring a simple clinical question to a much more complex real-life situation. Confounding factors must be eliminated but the trial must not become a theoretical schematic exercise, because that would only produce improbable patients followed through implausible procedures, with inflexible therapeutic methods, that will give results that cannot be transferred anywhere.

People responsible for drafting the protocol
Principal investigator(s) (Chair/Co-chairs)
Person responsible for study coordination/monitoring
Clinical trial specialist
Statistician
Data manager
Other clinicians participating in the trial

People responsible for drafting the protocol
Representatives of the promoter/sponsor or firm(s) supplying the treatment(s)
Pharmacist
Laboratory technician
Community/patients' representatives
Clinical or diagnostic specialists, depending on the topic being investigated

Main protocol headings
Title
Version and date
Principal investigator/protocol chair
Any changes from the original/previous version
Contents
Summary
Flow-chart (times, scheduled visits and procedures)
Background and rationale
Purpose, aims and design

Treatment(s) selected: preclinical and clinical information on the drugs: activity, toxicity, pharmacokinetics
Design: randomization, controls, blinding, placebo, phase
Duration and population, inclusion and exclusion criteria
Selection and withdrawal of patients
Treatment regimens
Primary and secondary endpoints
Measures of efficacy
Measures of safety

Concomitant therapies admitted
Participation in concomitant trials
Statistical details, sample size and data analysis
Screening procedures
Entry procedures
Follow-up procedures
Definition of treatment failure and relative procedures

Adverse events: definition, grade and severity
Procedures for reporting and managing serious adverse events and deaths
Treatment changes to cope with adverse events
Withdrawal from the trial, interruption of treatment, and subsequent follow-up
Sample collection and special instrumental investigations
Direct access to source data and documents

Sub-studies
Quality control and assurance procedures
Committees and other structures involved in the trial conduction

Verifying trial progress: enrolment, follow-up, performance of the centers
Interim analysis and stopping the trial
Ethical aspects, confidentiality and insurance
Investigator’s responsibilities
Monitoring and audits
Data handling and document storage

Financial matters

Data ownership and publication

Bibliographic references

APPENDICES:
Grading adverse events
Criteria for defining the endpoints
Patients' information sheets (version and date) and written informed consent forms
Letter for the patient's usual practitioner

ENCLOSURES:
Investigator’s Brochure on the drug(s) on trial
Case report forms (CRFs)
Contract
Insurance
Operating procedures

The operating procedures comprise all the specific documents that may need to be consulted frequently during the trial but are not already part of the protocol.
They contain precise information such as names, addresses, telephone numbers, codes for test-tubes or materials, instructions and details for various activities.
These are the details needed for the operations referred to in general terms in the protocol.

The Coordinating (Steering) Committee

It is generally preferable for the decisions and responsibilities in a clinical trial to be shared rather than centered on one individual. The role of ethics committees

is covered separately in this book, so it may be useful here to summarize the collegial structures sometimes needed in a trial. Although those mentioned here are mainly needed for large trials, some basics are common to all studies, so it is worth looking at the specific tasks of some of these bodies.

Specific committees for a clinical trial
An independent Data and Safety Monitoring Committee (DSMC) to follow the trial
Coordinating (Steering) Committee
Executive group for study management: checks the progress of the trial and the relations between the various parties
Groups for conducting sub-studies
Committee/group for clinical review of events
Committee/group for data handling: defines the various aspects of data handling, the common database, and deadlines for data transmission and analysis
Quality control committee
Communications committee (e.g., newsletters, press communiqués)
Patients' representatives committee

Independent committee for trial monitoring (DSMC)

This is the Data and Safety Monitoring Committee, whose members must be independent people not connected with the trial; they must have clinical or statistical skills and must be free to follow the trial directly with periodic evaluations (normally every 4-6 months for mid- to long-term studies). As the DSMC can stop a trial if necessary, it must be able to assess the findings in open conditions; this means the procedures for data collection, management and analysis must be planned so the DSMC has access to the interim trial findings, as part of the general planning for interim and final analysis (final study report).

The DSMC's responsibilities for deciding whether to continue a trial thus obviously include "internal" aspects such as interim analysis of whether differences in the efficacy of treatments exceed the limits set as significant, and whether recruitment and follow-up are proceeding as scheduled; they also include checking the pertinence of the trial in its general context, by assessing any new information that suggests the trial should not be continued because there is no longer uncertainty about the efficacy or toxicity of the treatments being investigated.

Endpoint review

The importance of the people who have to review and validate the endpoints should not be underestimated. Once the monitor has collected the documentation and verified it against the source documents, it has still to be checked in the light of the criteria established for the endpoints.

Data handling

Data handling is often erroneously considered a matter than can be dealt with fairly late, towards the end of a trial. However, like everything else, some aspects have to be agreed from the start and data collection must be planned so as to give useful findings for analysis. For example, it may not seem immediately evident, but a poorly designed data collection form will provide poor-quality information that is hard to analyze properly – and often impossible to re-construct later!

The coordinating center’s tasks (which can be delegated to a CRO)
General secretariat
Checking how the protocol is being implemented
Clinical aspects and pharmacovigilance
Data handling and analysis
Monitoring
Drug handling
Logistics and sample handling
Administration and contracts