DRAFTING A CLINICAL STUDY PROTOCOL

AN OVERVIEW

INTRODUCTION

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), a clinical trial is "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous."

Amongst the various parameters, contributing towards delivering successful clinical trials, a well-defined clinical study protocol (protocol hereafter) is an essential one. It constitutes the essential documents required in clinical trials along with the Investigator's Brochure (IB), Subject Information and Informed Consent Form (ICF), Case Report Form (CRF) and Clinical Study Reports (CSR).

This article presents a brief overview on protocols in pharmaceutical clinical trials, by addressing the following questions:

- What is a clinical study protocol?
- Why is a clinical study protocol important?
- When is a clinical study protocol drafted?
- Who drafts a clinical study protocol?
- How is a clinical study protocol drafted?
- What are the constituents of a clinical study protocol as per ICH-GCP?

What is a clinical study protocol?

It is "a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments."

Why is a clinical study protocol important?

Every clinical investigation begins with protocol development. Apart from being the foundation of clinical trials and aiding in research preparation, a protocol also serves as a tool for controlling quality of the entire research.

WELL-DEFINED, PRACTICAL AND DETAILED PROTOCOLS, ARE OF PARAMOUNT IMPORTANCE AS THEY:

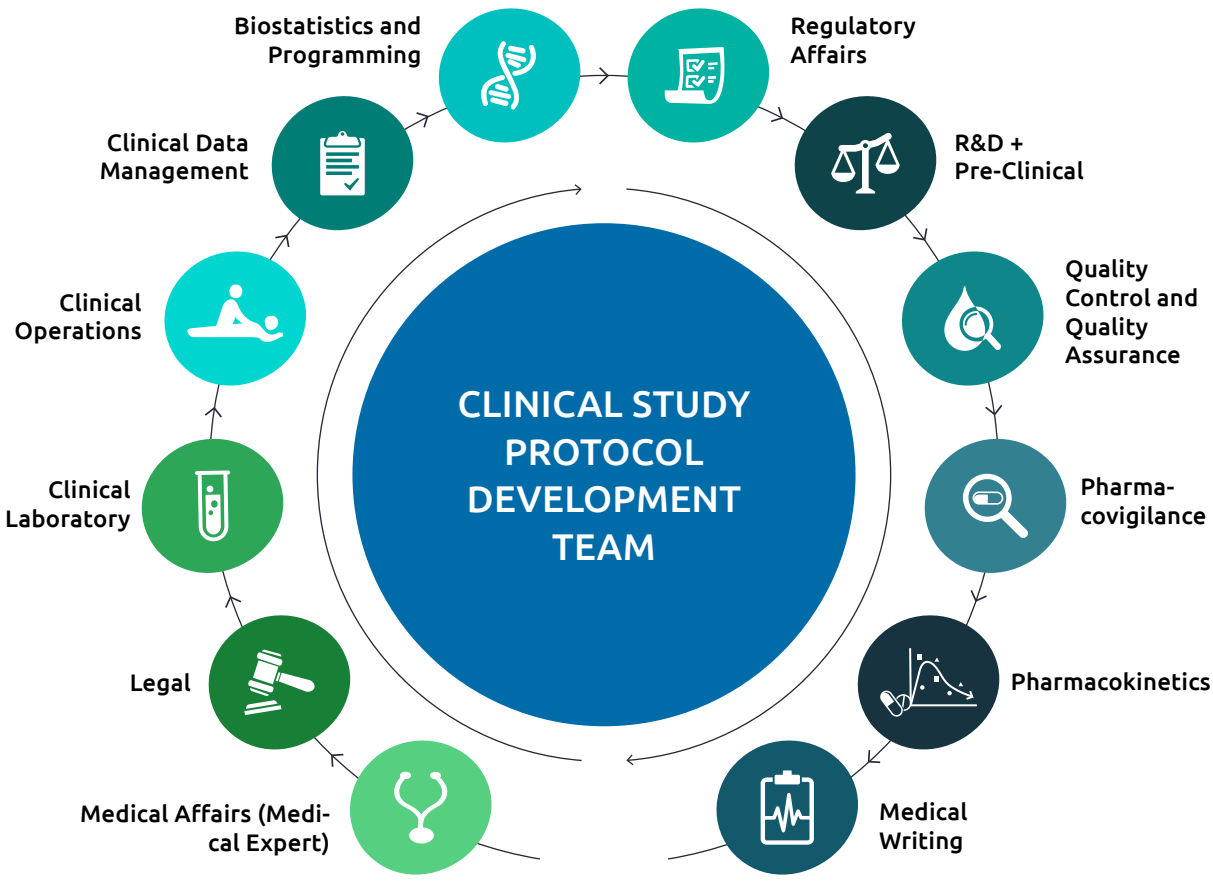
- **Reduce probability of queries** generated during review by Regulatory Authorities and Ethics Committees, thus aiding in on-time clinical trial completion
- **Act as a guide on the documents and data points** to be collected, verified, validated and maintained in alignment to the clinical trial
- **Prevent misinterpretation** amongst trial team members by acting as a single source of reference, on the clinical trial related activities, timepoints, procedures etc
- **Enable uniformity in the conduct of the clinical trial** (be it amongst trial team members in the same site or across multiple participating trial sites)
- **Generate credibility** in the scientific community
- **Allow replication by other researchers** who may wish to take the research forward or design clinical trials along the same lines
- **Give assurance of a patient's** – a) voluntary participation, b) safety being of prime focus amongst other factors

When is a clinical study protocol drafted?

A protocol is the first document that is drafted when designing and planning a clinical trial. All other related/involved documents (like patient diary), templates/forms (like CRF), digital interventions (like wearables) etc are in alignment to the details stated in the protocol.

Who drafts a clinical study protocol?

Designing a protocol, is a teamwork, necessitating involvement of subject matter experts (SME) from multiple teams, some of them being:



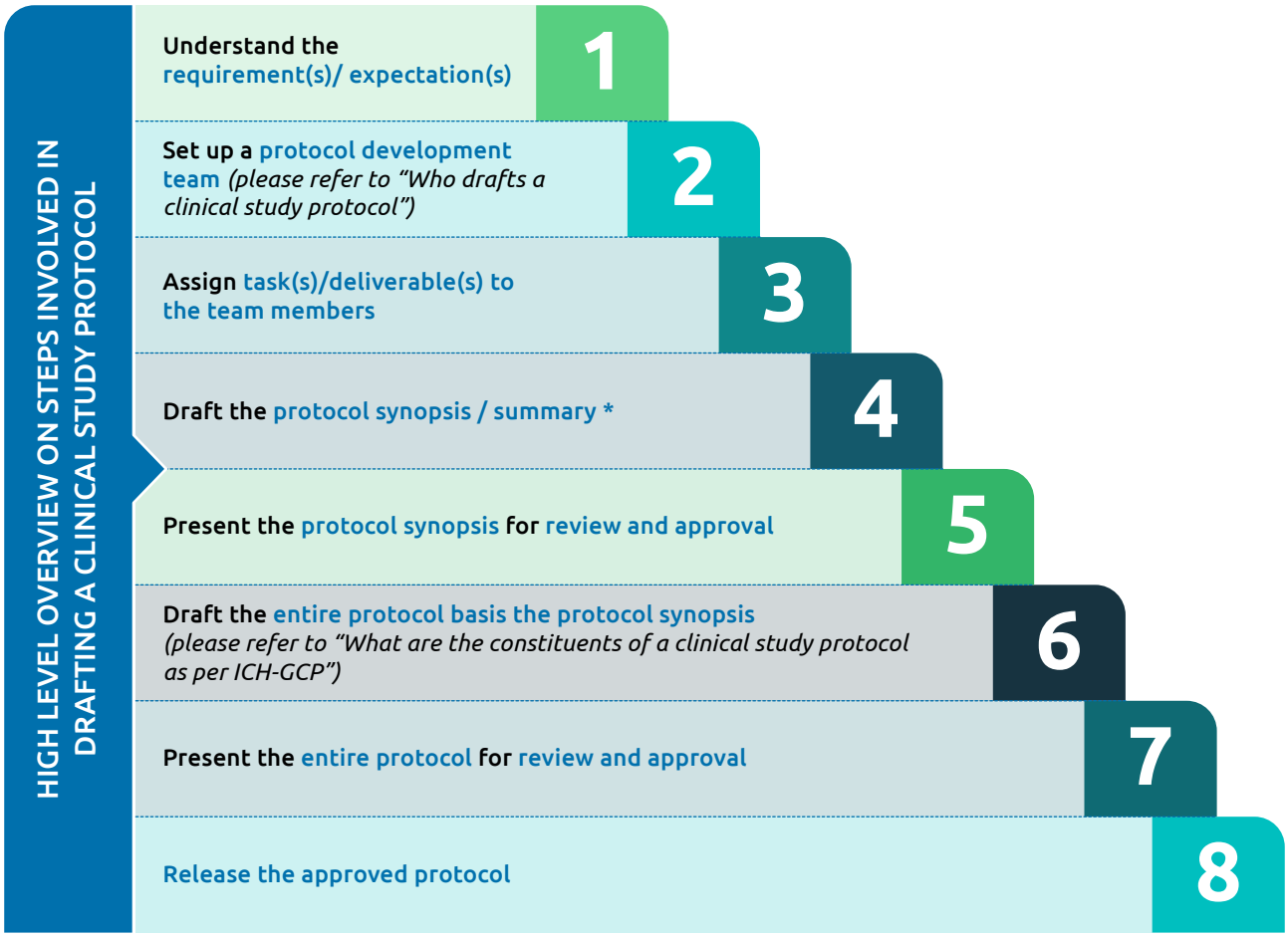
While SMEs contribute in alignment to their areas of expertise, the Medical Writer is responsible for compiling received inputs from the various SMEs to draft the: a) Protocol synopsis or protocol summary document and b) Clinical study protocol.

The end-to-end process of protocol design and development is spearheaded by the Medical Expert, who is ultimately responsible for this activity.

How is a clinical study protocol drafted?

When drafting a clinical study protocol, it essential to ensure compliance to the ICH GCP E6 guidelines along with the geo specific regulatory requirements. For example, a clinical trial to be conducted in India, will require the corresponding clinical study protocol to be compliant to ICH GCP E6 guidelines and Central Drugs Standard Control Organization (CDSCO) requirements.

There are several steps involved in the design and development of a protocol. Illustrated in the diagram below is a high-level simplified representation of the same .



*** A protocol synopsis / summary should contain at minimum information on**
a) Objective(s), b) Endpoint(s), c) Design, d) Schedule of events and assessments, e) Inclusion-Exclusion-Withdrawal criteria, f) Screening and enrolment, g) Safety assessments, h) Efficacy evaluations, i) Pharmacokinetics sampling if involved etc

WHAT ARE THE CONSTITUENTS OF A CLINICAL STUDY PROTOCOL AS PER ICH-GCP?

Section 6 of the E6 Good Clinical Practice (GCP) guidelines discuss on the contents of a clinical trial protocol and amendment. For ease of understanding, the pointers included therein, at a high-level can be categorized as :

Using the high-level categorization (in the diagram above), a clinical study protocol, as per ICH-GCP should include detailed information (description, justification, schematic diagram, process etc, as appropriate) on the following at minimum:

Contact details related

- Name and address:
  a) Sponsor, b) Monitor (if other than the sponsor), c) Investigator(s) responsible for conducting the trial, d) Trial site(s), e) Clinical laboratory(ies), f) Other involved medical and/or technical department(s), g) Other involved institutions
- Name and title:
  a) Authorized signatory
- Name, title, address and telephone number(s):
  a) Sponsor's medical/dentist (depending on the trial indication), b) Physician/ dentist responsible for all trial-site related medical/dental decisions (if other than investigator(s))

Trial related

- Tile
- Number
- Date of effectiveness
- Amendment number
- Amendment Date
- Summary of relevant findings:
  a) Nonclinical studies, b) Clinical trials, c) Known and potential risks and benefits to human subjects, d) Literature and data
- Objectives
- Purpose
- Endpoints (primary and secondary)
- Type/design
- Sequence of events and assessment
- Bias management (randomization, blinding)
- "Stopping rules" or "Discontinuation criteria" (partial and complete)
- Study population
- Trial treatment-Investigational product(s)/ Comparator(s)/Placebo(s) involved
- Medication(s)/treatment(s) – Prohibited and Allowed (including rescue medication)
- Confirmatory statements:
  a) Investigator(s)/institution(s):
  a1) permitting a) trial-related monitoring, b) audits, c) IRB/IEC review, d) regulatory inspection(s), a2) providing direct access to source data/documents
  b) Conducting the trial in compliance with the protocol, GCP and the applicable regulatory requirement(s)

Participant related

- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria
- “Stopping rules” or “Discontinuation criteria”
- Treatment(s) to be administered
- Duration of participation

Treatment related

- Name
- Description
- Route of administration
- Dosage
- Dosage regimen
- Treatment duration
- Packaging
- Labelling
- Follow up
- Accountability

This includes the Investigational Product(s), Comparator(s) and/Placebo(s)

Safety related

- Identified parameters
- Methods for assessment
- Timing of assessment
- Recording assessment result(s)
- Reporting result(s)
- Adverse event management
- Intercurrent illness management

Efficacy related

- Identified parameters
- Methods for assessment
- Timing of assessment
- Recording assessment result(s)
- Reporting result(s)
- Adverse event management
- Intercurrent illness management

Data management and biostatistics-programming related

- Statistical methods
- Interim analysis
- Sample size
- Power of the trial
- Level of significance
- Trial termination
- Missing, unused, and spurious data
- Deviation(s) from the plan
- Subject selection for analyses
- Code maintenance
- Code breaking
- Data to be recorded directly on the CRFs

Trial monitoring and management related

- Subject compliance
- Quality control
- Quality assurance
- Ethical considerations
- Data handling
- Record keeping
- Insurance
- Publication
- Other supplements

CONCLUSION

Consequences of poorly designed and drafted protocols for clinical trials are costly, potentially leading to:

- Queries from Regulatory Authorities, Ethics Committees etc during their review
- Risk to health and/safety of volunteers (patients) participating in the clinical trials
- Release of multiple protocol amendments
- Decision or instruction to terminate the clinical trial
- Extension in completion timelines of the clinical trial
- Increase in cost of conducting the clinical trial
- Non-approval by the Regulatory Authorities of the data generated and analysis made therein etc

At Capgemini, we have years of experience in designing clinical trials and subsequently drafting them as clinical study protocols. Supported by our in-house smart trial platform, our experts can help develop protocols that are detailed, patient-centric, operationally feasible, well-rounded and in compliance to the applicable regulatory and other binding requirements.

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