

Peer review of a clinical trial protocol: Practical tips for regulatory medical writers, clinicians, and clinical scientists

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Abstract

Protocol development is a critical milestone in the clinical drug development process for all pharmaceutical companies conducting clinical trials. A regulatory medical writer (RMW) plays a crucial role in the protocol development and peer review processes along with different stakeholders. Poor peer review leads to protocol amendments, which delay regulatory submission and increase project costs. Thus, there is a strong need for RMWs and stakeholders to work together during the peer review process to highlight the specific issues that should be addressed before finalisation, which helps in creating effective, efficient, and high-quality protocols. The suggested protocol peer review steps described in this article will help an RMW to plan, coordinate, and deliver this highly important document for global and local clinical trials.

Introduction

Clinical trial protocol development and peer review processes are vital to the clinical development programme of pharmaceutical companies and contract research organisations (CROs). These processes result in the successful submission of a systematically reviewed clinical trial protocol to regulatory authorities for their expert opinions and approval.¹ The clinical trial

protocol peer-review process is where many “experts” examine the proposed trial to consider aspects such as study design, trial procedures, subject eligibility, feasibility, acceptability, and study endpoints.^{2,3,4} A review of the clinical trial protocol by scientific experts is crucial for a regulatory medical writer (RMW) to generate a high-quality protocol for regulatory submission.⁵ Hence, an RMW needs a comprehensive understanding of the peer-review process and steps⁶ that must be followed during the peer review of a clinical trial protocol and other clinical regulatory documents. Therefore, we have made an effort to provide practical advice to an RMW regarding the peer review process of the clinical trial protocol to enhance the value and efficiency of the protocol review process. This process will help to avoid poor review practices in pharmaceutical companies, CROs, and knowledge process outsourcing (KPO).

Peer review process

Peer review is a process in which subject matter experts review each other's work to meet the accepted high standards of their discipline and disseminate research data to ensure that unwarranted claims, unacceptable interpretations, or personal views are not presented without prior expert review.²

The peer-review process can be inefficient and challenging for writers and peer reviewers when there is a communication gap between the two. Thus, effective coordination between peer reviewers (stakeholders) and RMWs is essential to ensure that the peer-review process runs efficiently. The peer-review team (Figure 1) and the peer-review process (Figure 2) add substantial value to the clinical protocol development (Figure 3). In this process, stakeholders are responsible for the design, scientific aspects, regulatory, ethical and legal requirements of the protocol, and RMWs are accountable for ensuring the consistency,

accuracy, formatting, and finalisation of the protocol.^{3,7,8}

We list below steps for RMWs to encourage efficient review of the protocol within the pharmaceutical industry, CROs, and KPO. It is also recommended that all stakeholders follow these tips for an efficient review.

Peer reviewers in a clinical protocol development

Different stakeholders play a vital role during the peer review of the clinical protocol. The various stakeholders and their expertise for the protocol review are presented in Table 1.^{1,7,9,10,11}

The peer review team composition can vary depending on the type of study and study design (Figure 1).

The peer reviewers should consider the crucial elements for an effective peer review, which will help develop a high-quality protocol (Table 2).

Kick-off meeting

The RMWs and stakeholders must collaborate effectively during the peer review process. The

When developing a global clinical trial protocol, the stakeholders may be located in different locations; hence the kick-off meeting is usually organised virtually.

best way to collaborate and communicate during the peer review process is to set up a kick-off meeting^{1,12} with all the stakeholders to understand the roles and responsibilities of the team members, training needs, data sources for review, instructions and expectations about the review, maintaining meeting minutes and action items, the review cycles, the timelines, and comments resolution process. When developing a global clinical trial protocol, the stakeholders may be located in

different locations; hence the kick-off meeting is usually organised virtually. An RMW should know the time differences in different countries to achieve a robust peer-review process. An RMW must consider the following steps before, during, and after a kick-off meeting:



Before meeting:

- Consider the various time zones where the team members are located. Confirm a virtual meeting time with different stakeholders through e-mail before sending any meeting invitation.
- Ensure that each particular protocol section's responsible subject matter experts are identified and invited to the meeting.
- Ensure that all invitees have access to the virtual meeting platform.
- Have all the virtual meeting details (time, link, participants' details, agenda, protocol

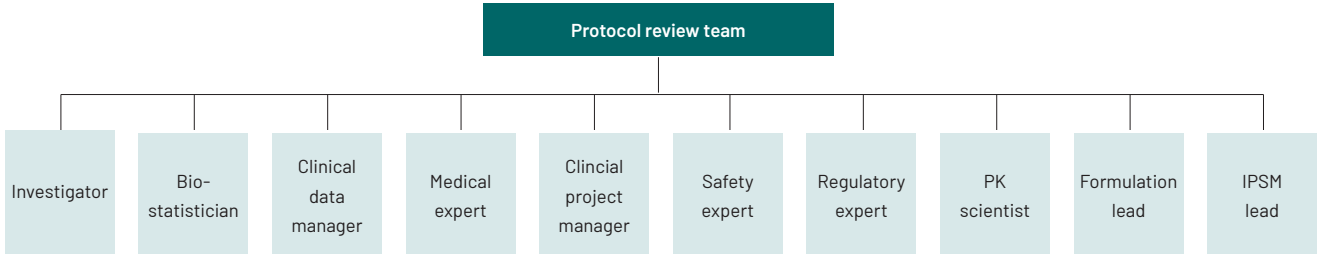


Figure 1. Recommended clinical protocol peer review team composition

Abbreviations: PK, pharmacokinetic; IPSM, investigational product supply management

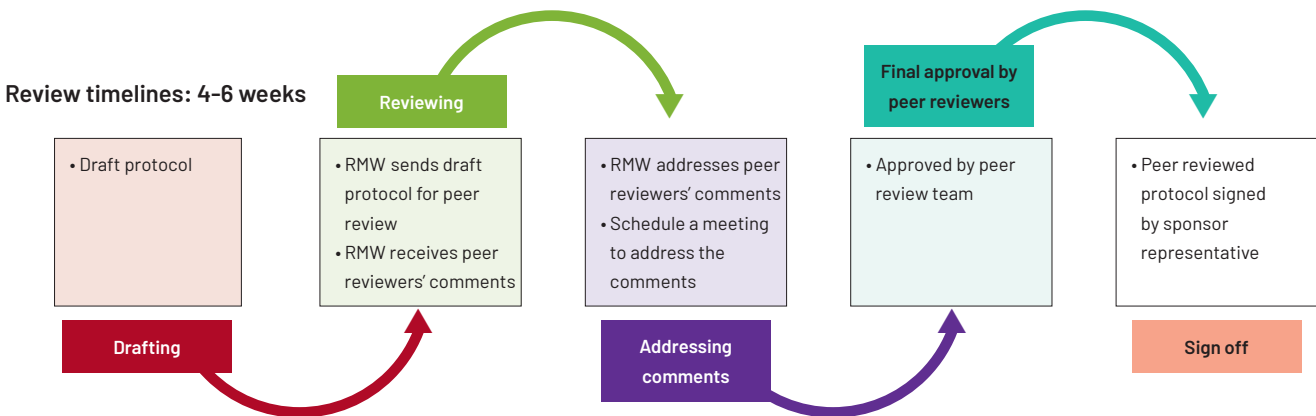


Figure 2. Recommended clinical protocol peer review process flow

Abbreviation: RMW, regulatory medical writer

Table 1. Stakeholders and their opinions on protocol review

Peer review team composition and their opinions on key elements	Peer review team composition and their opinions on key elements
1 Investigator <ul style="list-style-type: none"> ● Feasibility of a trial ● Trained and experienced resources ● Significant risks in a trial ● Inclusion and exclusion criteria of patients ● Operational challenges ● Benefit and risk ratio in the current trial 	5 Clinical project manager <ul style="list-style-type: none"> ● Description of study conduct ● Feasibility of a trial ● Optimal execution of a study ● Operational challenges
2 Medical expert <ul style="list-style-type: none"> ● Study design ● Inclusion and exclusion criteria ● Primary and secondary objectives ● Endpoints ● Assessment procedures ● Use of concomitant therapies or the stopping rules to be applied in the study ● Scientific expert on regulatory queries and their responses ● Operational challenges 	6 Safety expert <ul style="list-style-type: none"> ● Description of the drug surveillance program, including medical reviews for safety reporting, safety databases, necessary follow-up, risk assessment, and products relatedness
3 Biostatistician <ul style="list-style-type: none"> ● Statistical procedures, methods, and interpretation of endpoints ● Safeguards the minimisation of potential variability in the study ● Precautions to prevent various forms of bias in the protocol 	7 Regulatory expert <ul style="list-style-type: none"> ● Ensure compliance with the FDA and international regulations/interpretations/guidelines for designing and conducting a clinical trial protocol
4 Data manager <ul style="list-style-type: none"> ● Key data items to be collected and the frequency of collection with respect to the visit schedule for the development of paper Case Report Form (CRF) or eCRF ● Ensure that data elements are complete and reliable ● Identify any missing key data elements in a protocol 	8 Pharmacokinetic (PK) scientist <ul style="list-style-type: none"> ● Description of PK objectives and endpoints, dosing procedures and dosing frequencies, PK requirements, and statistical procedures for evaluating PK data
	9 Formulation lead <ul style="list-style-type: none"> ● Ensure adequate preparation and form of a drug, which is both stable and acceptable to the patient throughout the study
	10 Investigational product (IP) supply management lead <ul style="list-style-type: none"> ● Description of good manufacturing practices for preparing, storing, packaging, labeling, and distributing the IPs to the study sites

synopsis/outline/concept sheet, and other source documents) ready one day before the meeting. Check the technical functions of the virtual meeting technologies beforehand to avoid technical glitches during a meeting.

- Confirm the contact details and availability of the attendees.
- Prepare a checklist before initiating any kick-off meeting to facilitate a productive discussion.

During meeting:

- Ensure having a stable internet connection and clear audio during the virtual meeting. Important information can be missed in case of audio issues.
- Remember to mute yourself if you are not speaking.

- Listen carefully to the discussion and take notes for future reference.

After meeting:

- Prepare the meeting minutes and distribute them to help all stakeholders for the next meetings. The meeting minutes will help the team with further actions and planning.

Tools and techniques for peer review

Version control

The version control of the clinical protocol is a crucial step in the peer review process. In many cases, an RMW receives multiple versions/texts from different stakeholders as e-mail attachments/e-mail texts.⁶ This poses challenges to keeping track of various versions, consolidating comments, and reconciling issues in the next

draft of the protocol. The RMW can potentially miss essential comments from the critical reviewers, leading to poor protocol quality. Thus, the review team should use common document management tools as an effective method to maintain the versions of the protocol during the peer review process.

Document management systems

As per Good Clinical Practice (GCP), the sponsor should validate all the computerised systems based on a risk assessment that considers the system's intended use and the system's potential to affect human subject protection and the reliability of trial results. Hence, GCP-compliant systems are essential in the peer review process. A lot of electronic tools⁶ are available to perform the peer review of the protocol/other



Figure 3. Significance of peer review in clinical protocol development

documents, which will help to achieve effective review and version control of the protocol. Below is a non-exhaustive list of potential tools.

- Veeva Vault
- PleaseReview
- Citrix Software
- Shared Network Directory
- Lotus Notes
- Documentum/Document Management Software

The above document management systems support the serial review process where all the reviewers can review the documents simultaneously and see comments from other team members. These document management systems show who checked out the document, when and when it was checked back in and

keep track of versions and updates in the document management system. It is essential that a system available and familiar to all stakeholders is used.

Comments resolution and conflict management

The clinical trial protocol development is crucial in running a critical trial. An RMW should be well-versed in international requirements, regulatory guidelines, templates, and style guides. It is essential to provide training materials, standard operating procedures (SOPs) (sponsor’s SOPs and CRO’s SOPs), work instructions, and other guidance documents necessary for protocol development.

An RMW should consider the following recommended techniques to manage the

demanding situations for the peer review process of the protocol.

Structured comments/review technique

An RMW should clarify what they want the reviewers to focus on and how comments should be added to the protocol during the kick-off meeting for a focused and effective review. Generally, a strategic review is needed to focus on the data’s content and scientific validity. It should not focus on inconsistencies, numbers, spelling errors, abbreviations, language, editorial, style, citations, cross-references, and overall formatting.

Early delivery technique for the review

There may be situations wherein the peer review of the protocol was delayed due to the complex

Table 2. Crucial elements to consider during peer review of a protocol ^{7,8}

Section	Crucial elements for peer review
Introduction	<ul style="list-style-type: none"> a. Current prevalence and incidence of disease b. The rationale for the choice of study design elements c. The goals for doing this particular study at this point d. Description of research question and justification for undertaking the trial, including a summary of relevant studies e. An unmet medical need for any indication f. Known and potential risks and benefits g. An explanation for the choice of comparators h. Drug and disease-specific background information, including the safety information available i. Competing products on the market
Objectives	<ul style="list-style-type: none"> a. Should present the question(s) that the study is designed to answer b. Verify clearly whether the trial is planned for superiority, noninferiority, exploratory, and scientific rationale for these
Evaluations and endpoints	<ul style="list-style-type: none"> a. Evaluate the necessity to conduct this trial at this stage b. Evaluate the necessity to combine this trial with another trial, if applicable c. Do the endpoints support the objectives of the study? d. Are the endpoints clinically and scientifically valid for the disease being studied? e. Are the estimands clearly indicated? f. Are the endpoints chosen the best ones to measure? g. Verify the tools, instruments/questionnaires, and laboratory tests that will be used to gather the data for the efficacy endpoints h. Review evaluations required for both primary and secondary endpoints i. Review the references for the development and validation of instrument content j. Verify the patient population in which the questionnaire was validated, with special attention to the current study population k. Verify the specific time points and their acceptability to the regulatory authority (e.g., change from baseline to Week X). Consider including the definitions of the derivation, use, and timing of a composite endpoint
Hypothesis	<ul style="list-style-type: none"> a. Types of hypotheses used in the trial and reasons for the selection b. Verify whether any hypothesis is stated in the protocol. If not, a convincing reason not to state a hypothesis should be verified in the protocol c. Statements of hypotheses should consider the endpoints being studied, including the time at which the endpoints are measured, such as the day or week or specific visit d. The hypothesis should not be a rewording of the objectives. Verification of the study hypothesis is a very important aspect of the study. Review this carefully.
Study design	<ul style="list-style-type: none"> a. Is the design itself the best one for this trial? Why? Have the authors considered other designs? b. Can the chosen design control major sources of bias? c. What is being done to minimise the placebo response? d. Feasibility for patients and doctors e. Does it have to be randomised? If so, why? f. Method of assigning treatment to subjects (e.g., randomisation) or other measures to be taken to minimise bias, including key stratification variables g. Level of blinding (e.g., open-label, double-blind) h. Competition for this trial, for the patient population, for institutions, and for industry trials i. If a specific study setting is required, please describe (e.g. community clinic, tertiary care hospital) j. Explanation of sequence and duration of study phases/periods, including any follow-up phase, and expected duration of subject participation k. Review the end of study definition l. Choice of control: If an active control is used, indicate whether the intent is to establish superiority, noninferiority, or equivalence of the study drug under investigation compared with the active control m. The rationale for choosing the study population, level of blinding, treatment groups, dosage and dose administration interval, route of administration, treatment period, control selection, efficacy measures, length of study phases and periods

Section	Crucial elements for peer review
Time and events schedule	<ul style="list-style-type: none"> a. Review the efficacy and safety parameters, pharmacokinetic, pharmacodynamic, biomarker, pharmacogenomic, immunogenicity, or other measurements and their frequency/timing, regarding the time and events schedule b. Can any procedures be eliminated or reduced in number/frequency? c. Can any patient visits be eliminated? d. Can any tests conducted at any visit be eliminated? e. Does the protocol list what is to be done at each visit? f. Do the patient visits and assessments match those presented in the Table of assessments?
Eligibility criteria	<ul style="list-style-type: none"> a. Are they necessary for the trial? b. Is this reasonable? Are they too restrictive? If so, can they be relaxed? Not restrictive enough? c. What about other health problems (for example, diabetes)? Could some be eligible? d. Life expectancy criterion – what is it based on? Is this necessary? e. Are there any inclusion criteria that can be eliminated? f. Are the inclusion criteria going to create the most appropriate group of patients regarding the ability to extrapolate the data? g. Are the inclusion criteria realistic in terms of patient recruitment?
Patient population	<ul style="list-style-type: none"> a. Is the population to be studied the most relevant one to meet the company's goals? b. Does the study population have appropriate gender and minority representation? c. Does the study population contain elderly patients? (Should it?)
Blinding (if applicable)	<ul style="list-style-type: none"> a. Is this issue adequately addressed? b. Are all groups blinded that should be blind (i.e. those who interact with the primary investigator, patients, staff at the site, and sponsor)? c. Does the protocol adequately deal with the question of blinding the drug container, packaging labels and how to unblind patients in cases of problems?
Concomitant therapy	<ul style="list-style-type: none"> a. Does the protocol deal appropriately and adequately with this issue? b. Does the protocol list acceptable and unacceptable prescription drug therapy, over-the-counter drugs, and other nonprescription products and the terms under which each may be used?
Patient compliance	<ul style="list-style-type: none"> a. Is patient compliance being monitored or measured in this trial? If so, how? b. Is this the best way, and have other ways been considered?
Safety reporting	<ul style="list-style-type: none"> a. Ensure the compliance of country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards /independent ethics committees, and investigators
Pregnancy reporting	<ul style="list-style-type: none"> a. Ensure the compliance of collection of pregnancy information and reporting of pregnancy, including abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
Contraception guidelines	<ul style="list-style-type: none"> a. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
Data protection	<ul style="list-style-type: none"> a. Is the data protection section included in the study protocol? b. Ensure compliance with the applicable rules on the protection of personal data and any relevant information on measures to be taken in case of a data security breach
Start and end of study	<ul style="list-style-type: none"> a. Is the clear end-of-study definition included in the study protocol? b. Is the clear study completion definition included in the study protocol? c. Verify if there is any difference in the end-of-study definition and study completion definition as per regulatory requirements
Stopping criteria	<ul style="list-style-type: none"> a. Verify a description of the stopping rules or discontinuation criteria for individual subjects, study periods of the clinical trial, and the entire clinical trial
Compliance with ethical and regulatory requirements	<ul style="list-style-type: none"> a. Is the study protocol designed and developed in compliance with applicable ethical and regulatory requirements? b. If applicable, does the study protocol follow specific guidance documents for specific indications or therapeutic areas?



work environment and conflicting resources with projects. Delays can lead to poor protocol review due to insufficient review time. Thus, an RMW should coordinate with all the stakeholders and target to complete the peer review process before the delivery date (2 to 3 days before the review timeline). This will enable the completion of the protocol on time.

Comments management techniques^{1,13}

Too many reviewers can lead to conflicts and contradictions. An RMW can propose to minimise the number of reviewers (one subject matter expert per function) during the peer review. If there are multiple reviewers per function, an RMW can request a consolidated set of comments per function, with one contact person coordinating per function.

The best way to resolve comments is to set up a comments resolution meeting¹ with all the stakeholders. Differences of opinion should be discussed openly till a consensus is reached.

Crucial instructions/ expectations technique for review

In many cases, the peer review process expectations are unclear to reviewers. Thus, an RMW should clarify the following expectations for the peer review of the protocol during their first meeting with the reviewers:

- Reviewers’ responsibilities, review process, and timelines

Too many reviewers can lead to conflicts and contradictions. An RMW can propose to minimise the number of reviewers (one subject matter expert per function) during the peer review.

- Familiarity with the current SOPs and current regulatory guidelines
- Familiarity with the data sources (protocol synopsis/concept sheet/outline, the current version of the investigator’s brochure, product label, a summary of product characteristics, and recent literature, if applicable)
- Instructions for electronic tools
- Familiarity with the document type and document development stage
- Expectations for categorisation of review comments

- Expectations for strategic input on content in the form of specific, actionable, and relevant comments
- Back-up plan for review
- Training requirement, if any

Training the reviewers^{1,6,12}

All the team members who are involved in reviewing a protocol should receive compulsory training for the following:

- How to review documents
- How to give comments (content-related, actionable, not editorial or stylistic)
- How to prioritise comments (critical, major, and minor)
- How to respond to other reviewers’ comments
- How reviewers should focus primarily on their area of expertise
- Training on electronic tools (confirm access, the familiarity of a tool, and difficulties)
- Any other training for new reviewers

Benefits of comprehensive peer review of a clinical protocol

Scientific support and benefits to the regulatory medical writer

All the peer reviewers are experts who provide scientific comments to the RMW. The success of peer review depends on each reviewer focusing on their area of expertise and trusting their teammates to focus on theirs. Peer reviewers should make changes in track change mode along with comment boxes that would be more helpful and efficient for a writer.

Scientific and technical support to different stakeholders

An RMW should be well versed with guidance documents, technical tools, medical and therapeutic area knowledge, language and grammar, regulatory, ethical and legal requirements, and formatting/editing tools. All the above skill sets and experiences are crucial in developing a good protocol, which will help all the stakeholders to achieve a significant milestone in the clinical development programme.

Support the regulatory team to achieve submission on time

A thoroughly reviewed protocol can avoid any significant protocol amendments, which will speed up the regulatory submission and save the project costs.

Summary

In summary, regulatory submission of a clinical trial protocol is a significant milestone for pharmaceutical, CROs, and other stakeholders in the healthcare industry. The demand for an

expert RMW who can accelerate such regulatory submissions with high-quality documents is increasing day by day across the globe. RMWs are an essential part of the protocol preparation and review team. The protocol peer review steps will help an RMW plan, initiate, coordinate, and complete the peer review process. Protocol development team members/stakeholders benefit from an RMW who understands the protocol development and peer-review process, stakeholder's roles and responsibilities, document management systems, and project timelines, which will help produce a high-quality document.

Conflicts of interest and disclaimers

The authors declare no conflict of interest. The opinions expressed here are solely those of the authors and not necessarily those of Sun Pharma Advanced Research Company Ltd.

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