An Insider's Insight into Concept Protocols

Concept protocols offer an excellent opportunity to capture your study design ideas, stimulate discussion with project teams on the fundamental aspects of a study and provide a means of achieving team alignment before investing the resources required to develop a full protocol. They are short, flexible documents that can be reviewed quickly and edited easily. However, this can encourage teams to develop multiple drafts. When do you stop? How many drafts should there be? What should you include?

We provide here some insights from the Niche clinical project management team who have been writing both concept and full protocols for commercial and non-commercial studies since 1998.

Before you start

Do you have a concept protocol document template to work from? If not, you could use the synopsis section from your full protocol template or you are welcome to use our template – simply send a request by email to the contact at the back.

Identify your concept planning and review team and invite them to take part. Keep the team small but remember to include relevant specialists who can contribute to discussions on aspects such as pharmacokinetics, statistics and safety.

Research similar projects and gather background information on study objectives and appropriate endpoints (including details on any exploratory biomarkers the measurement of which could inform future development strategy).

Prepare to succeed

Understand that a concept serves as a focus for identifying critical aspects of a study design and potential challenges. Concepts should stimulate discussion and achieve consensus on points that may cause delay in development of the full protocol.

Don't drag out the process of development by creating repeated drafts that change little more than minor details. Focus on the big picture. Once the team has finalised the concept it shouldn't take too long to develop a full protocol.

Keep the concept brief, do not put too much effort developing your first draft. A concept protocol is usually 6–8 pages long. Much longer and you start to lose the benefits associated with using the concept.

Key Insights

Full protocols take time to draft and review. It is well-established that the processes we use to develop protocols is imperfect and leads to a need for costly and delaying protocol amendments. Estimates suggest that nearly 60% of protocols require at least one substantial amendment, and nearly half (45%) of these amendments are avoidable [1].

The minutiae of a study's methodology and/or design often distract teams and delay protocol development. When it comes to discussing study delivery with sites it often leads to an extensive back-and-forth discussing the best design to operationalise it. Using a concept protocol makes it easier for all parties to focus on the important points relating to the study. A well-written concept protocol with full team and stakeholder buy-in will ensure the efficient development of a full protocol.

Concept protocols should be relatively short documents that can be edited easily. The content of a concept should be pruned to just the essentials - only the information necessary for a reviewer to appreciate the key objectives of the study.

Do not include information that might be considered as 'nice to have'. Furthermore, there are many standard paragraphs included in full protocols that you need NOT include in the concept protocol. Use a diagram to simplify complex dosing designs and foster ready understanding (Figure 1). One shortcoming of concept protocols is that teams can get distracted from their goal by repeatedly working on new drafts. Stay alert for version fatigue, don't drag out the process.

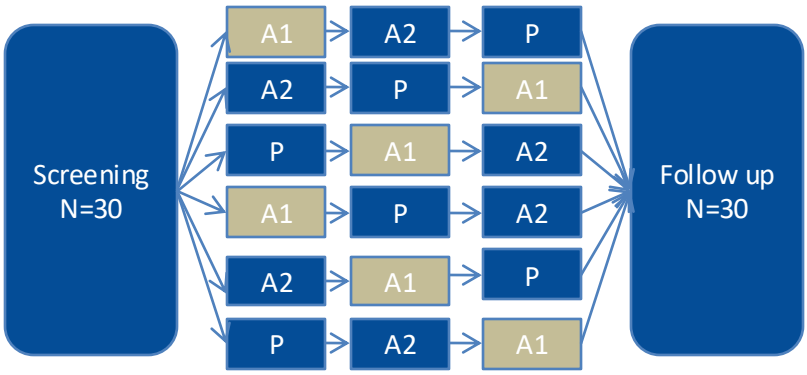


Figure 1: Study flow diagrams clarify complex designs
P=placebo; A1=Treatment arm 1; A2=Treatment arm 2

Identify your planning and reviewing team as early as possible so that you can confirm their commitment. Although the review team should be small, if you are planning an international study then it may be wise to get feedback from country representatives once key points have been agreed. Equally feedback on eligibility criteria from a small number of potential investigators can be very helpful.

Essential concept components include:

Background/study rationale: detailed reasoning for the study including an introduction to the investigational medicinal product (IMP), its development program and how the proposed study fits into it, why the study needs to be performed and how the outcome may be used.

Objectives: outline the primary, secondary and tertiary/exploratory objectives. Include only one primary objective that reflects the study hypothesis. Secondary objectives form the basis of additional analysis whereas exploratory objectives can be less rigidly defined and may be worded more loosely.

Endpoints: should be quantitative 'measures' that will inform whether an objective has been achieved.

Study design: briefly describes the elements of the study in no more than 2–3 paragraphs (unless the proposed study involves a multi-phase design). A diagram can help describe complex studies more clearly. Study stopping and subject withdrawal criteria should be included along with any rules relating to study adaptability.

Study population: should detail subject inclusion and exclusion criteria. The content will depend on the study population and the IMP's stage of development. The stricter the criteria the more homogenous the population but the harder it may be to recruit subjects.

Investigational product/intervention: provide details on the intervention to be undertaken and any differences between proposed study arms. Provide information on the route of administration, dose, treatment regimen and formulation type (e.g., capsule, tablet etc.) if a clinical trial involves IMP exposure.

Statistics/data analysis: provide the rationale behind statistical confirmation of the study's hypothesis including plans for analysis of the primary endpoint data. Also provide details of sample size calculations based on the primary endpoint and plans for analysis of the secondary and/or exploratory endpoints.

Study assessments: a time and events table can clearly define procedures and when they will be performed. Footnotes can be used (sparingly) to provide additional detail. Where necessary use more than one table to provide information on specific aspects of the study or procedures to be performed on intensive sampling days (e.g., pharmacokinetic sampling day in a Phase I study).

What NOT to include in the concept:

Site details – it can be useful to identify the region or country a study might be run in if there are only a few qualifying sites but lists of sites should be kept out of both the concept and full protocol.

Procedural or operational details – ideally these will not even make it to the full protocol. A study reference manual is a much better place for them. Study reference manuals do not require agency approval and have sufficient scope to allow authors to provide detailed information on procedural techniques. Modest changes can be made to how investigations are to be performed while the study is on going without introducing the need to amend the protocol.

Less is more

Clinical teams routinely add procedures guided by the belief that the marginal cost of doing so, relative to the entire clinical study budget, is small when the risk of not doing so is high [1,2]. Additional clinical data is collected as a precautionary measure in the event that a study fails to meet its primary and key secondary objectives as it may prove valuable in post-hoc analyses. Clinical teams also add procedures for fear that they may neglect to collect data requested by regulatory agencies and health authorities, purchasers and payers. A global analysis released by Phesi shows that many Phase III trials are often buried in excessive data due to overly complex protocols, impeding drug development and increasing patient burden. Collectively, these factors contribute to the marked increase in protocol design complexity that make designing study protocols difficult [3].

Possible team discussions

The landscape of clinical trial design is undergoing a transformative shift, driven by the integration of advanced technological solutions aimed at enhancing the efficiency, accuracy, and speed of trial protocol development. The purpose of the concept protocol is to stimulate team discussion over how to design a protocol that is feasible and can be delivered economically and efficiently. Points for the review team to consider include:

Background/Study rationale:

- Is the IMP or intervention under study closely related, chemically and/or in mechanism of action, to other compounds or procedures?
- Possible concerns about toxicological observations. Distinguish (a) direct effects due to the main pharmacological action, (b) known compound class adverse effects, (c) compound-specific effects
- What is known about the behaviour of the compound in man (pharmacokinetics, pharmacodynamics and tolerability), or, for first time in human (FTIH) studies, what to infer from animal work? Is the compound a substrate for a transporter? Consider metabolic pathways and metabolites (pharmacologically active, reactive etc.). For studies involving more than one compound (e.g., comparative or interaction studies) relevant information about each of the study medications should be considered

Study population:

- How subjects will be selected, the practicality of recruiting sufficient individuals who will meet the selection criteria and the possible identification and use of 'enriched populations' i.e., cohorts that include patients or subjects more likely to respond as hypothesised

Investigational product/intervention:

Dose selection:
- Are there any pharmacodynamic/preclinical data to support the choice of starting dose?
- For FTIH what method was used to calculate the dose? How reliable is any allometric scaling that has been used – such techniques can be unreliable for highly metabolised drugs
- Higher doses must be related to 'no observed adverse effect levels' in the most sensitive animal species. Is it desirable/necessary to explore the maximum tolerated dose in man? Choice of only a single dose level in later studies will need justification

Rationale for selecting a dose range to be explored:
- Will the study provide good dose-response information? Do the chosen doses cover a reasonable range of the anticipated dose-response curve? Do they take into account inter-individual variability?
- Is the trial design optimised to provide appropriate dose-response information? Will it provide dose-response data about side effects?

Study assessments:

- Planned assessments and their validation for measuring specific endpoints
- Does the trial design include sufficient monitoring for potential safety issues?

Statistics/data analysis:

- The rationale for the number of subjects and how data might be analysed
- Complexity of the protocol – there is a temptation to include as many measurements as possible but this has cost implications
- The chance of having to investigate unexpected findings resulting from assays not closely related to the main purpose of the study

An interview with one of our clinical project managers….

Q How long should it take to produce a first draft?

A You shouldn't invest too much time or effort in developing the first draft. Use the template to construct your outline where appropriate and include questions within the text that the team may address during their review. This way the team enters an iterative process of development – making progress with each new version over the next few days. Overall, the concept protocol approach should see marked reductions in the time it takes to develop the full protocol.

Q How do project teams respond to suggesting they adopt a concept protocol approach?

A There can be push back from some team members who see the concept as an unnecessary additional step. However, it is worth persisting as the quality of the final full protocol tends to be much higher. Review teams find it much easier to buy-in to key ideas and navigate past dead ends without additional regulatory nuances, clinical considerations and required duplication. Teams eventually accept the benefits associated with this approach.

Q What do you see as the main benefit of the concept protocol?

A Protocols are generally the product of multiple contributors –statisticians, clinicians, project managers and pharmacokineticists etc. An effective protocol – one that needs no amendment once it transitions into the operational phase – has integrated the interests of each of these contributors. The 'big picture' aspect of the concept facilitates discussion of the key factors and integrates the different 'interests' of each stakeholder before focusing on specific details required by each of the partners.

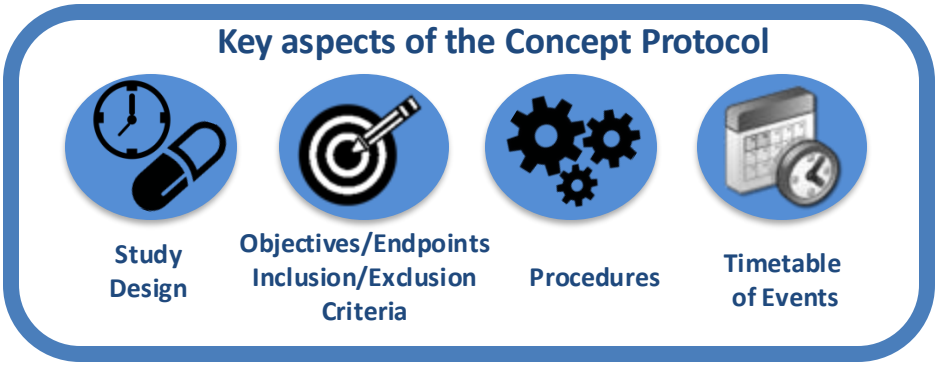
Q Are there any added benefits to concept protocols?

A Concepts are a great team-building opportunity. Team meetings can be brief, informative and productive. Development of a concept protocol is an iterative process. Concepts can be rapidly modified to capture site capabilities, patient demographics and other parameters that might lead to extensive protocol reviews and errors in site selection. Each draft brings the interests of the various parties closer together as they consider possible challenges to be faced in operationalising the study.

The impact of technology

Several companies report leveraging large language models (LLMs) to draft protocols by standardizing repetitive sections (such as inclusion/exclusion criteria or adverse event monitoring) and aligning language with regulatory guidelines, helping speed up initial protocol drafting. While specific success metrics for LLM-driven protocol drafting are not yet broadly available, initial reports suggest they reduce the time required for certain protocol sections [4]. However, integration of LLMs into clinical trial design processes remains in the pilot phase for most tech providers, with full-scale implementation requiring more validation and optimization to handle the complexities of trial protocols [5].

A few academic studies and case studies have examined how AI tools, including LLMs, perform in protocol drafting. One reviewed the potential of NLP models in improving clinical trial efficiency, showing promising results but also highlighted limitations, such as the risk of overlooking critical regulatory nuances and clinical considerations that require expert input [6]. Clearly, LLMs are successful in identifying redundancies and inconsistencies within protocol drafts but regulatory agencies like the US Food and Drug Administration and European Medicines Agency emphasise precision and human oversight in protocol development. Hence, LLMs are generally used in a supplementary role, assisting human experts rather than replacing them entirely. It is advised that when using LLMs in drafting your protocols you take into consideration the associated risks as defined in our Insider's Insight [7], and follow a conservative approach while recording where it has been employed and what permissions were sought for use.



And finally....

The design and development of clinical trial protocols are often characterized by complex, time-consuming tasks that require meticulous attention to detail and adherence to regulatory standards. Concept protocols are short, flexible documents that can be reviewed quickly and edited easily. However, they encourage teams to develop multiple drafts. When do you stop? How many drafts should there be? Don't drag out the process. Where at all possible, at the beginning of the process schedule a face-to-face meeting with the review team to finalise the concept. Keep the focus of the team on confirming the approach and agreeing on key points rather than deliberating on minor operational details and precise wording. Once the team has finalised the concept it shouldn't take too long to develop a full protocol.

References

1. Getz K, Zuckerman R, Cropp A, Hindle A, Krauss R, Kaitin K. Measuring the incidence, causes, and repercussions of protocol amendments. Drug Inform J. 2011;45:265–275.
2. Getz KA, Stergiopoulos S, Short M, et al. The Impact of Protocol Amendments on Clinical Trial Performance and Cost. Therapeutic Innovation & Regulatory Science. 2016;50(4):436-441.
3. Mostello G. Phesi analysis finds data overload slows down drug trials. NOV01, 2024 https://firstwordhealthtech.com/story/5908915
4. Ghim JL, Ahn S. Transforming clinical trials: the emerging roles of large language models. Transl Clin Pharmacol. 2023 Sep;31(3):131-138. doi: 10.12793/tcp.2023.31.e16.
5. Yseop Harness the Power of Gnerartive AI in Pharma: Accelerate Drug Discovery and Development. https://yseop.com/whitepaper-harness-the-power-of-generative-ai-in-pharma2/
6. Maleki M, GhahariSA. Clinical Trials Protocol Authoring using LLMs. arXiv:2404.05044 doi.org/10.48550/arXiv.2404.05044
7. Niche Science & Technology Ltd. Artificial Intelligence in Medical Writing: An Insider's Insight. 2024. https://www.niche.org.uk/asset/insider-insight/Insiders%20Insight%20GAILs.pdf

How can Niche help?

Our clinical project management team is experienced in preparing concept protocols across a broad range of therapeutic areas. We can coordinate review cycles and manage team comments remotely or through face-to-face meetings. Drafts can be turned around quickly, within hours if necessary. Our experienced study managers can bring their expertise to any team tasked with delivering a study and are always on hand to provide advice on the practicality of proposed study designs.

Next steps

We created this Insider's Guide to Concept Protocols to provide a few key learnings that we have acquired over the years. I hope you found this guide useful. If you would like a copy of our Concept Protocol template or would like further help or advice on writing your protocol please contact me at the email address below.

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