



## An Insider's Insight to 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 the Niche Science & Technology Ltd. template that can be downloaded <<here>>.

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 protocol serves as a focus for identifying critical aspects of a study design and potential operational challenges. A concept should be used to 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 with 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 that are associated with using a concept approach.

## Key Insights

Full protocols take time to draft and review. The minutiae of a study's methodology and/or design often distract teams and delay protocol development. 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.

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.

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.

## 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.

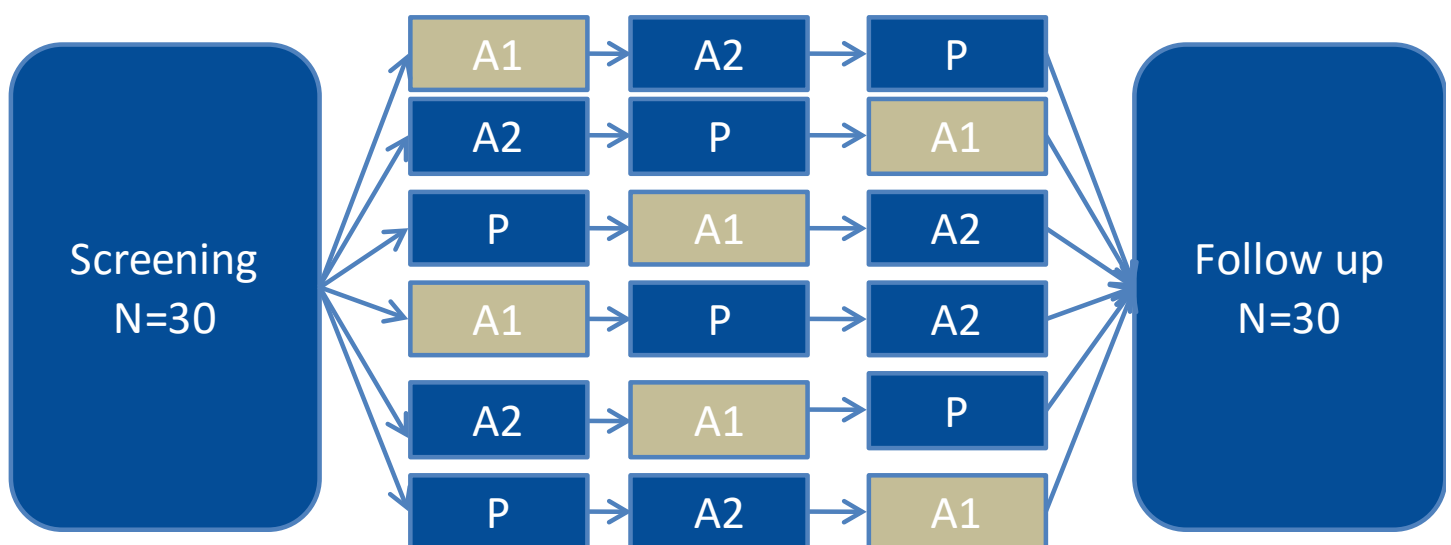
# Essential concept components include

**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 or not 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 (Figure 1). Study stopping and subject withdrawal criteria should be included along with any rules relating to study adaptability.



# Possible team discussions

The purpose of the concept protocol is to stimulate team discussion. 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. 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. Each draft brings the interests of the various parties closer together as they consider possible challenges to be faced in operationalising the study.

## Key aspects of the Concept Protocol



**Study Design**



**Objectives/Endpoints  
Inclusion/Exclusion  
Criteria**



**Procedures**



**Timetable  
of Events**

## And finally...

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.

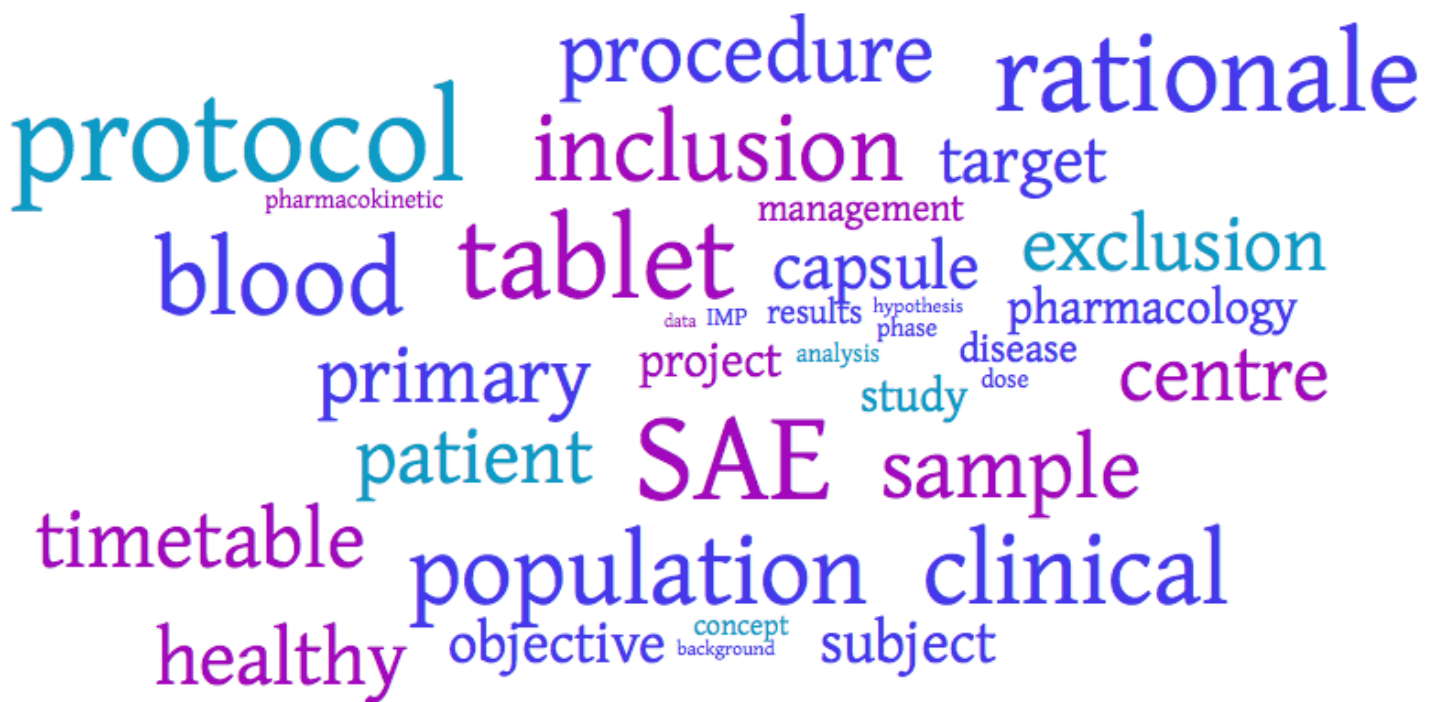
# How can Niche help?

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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