TAKE YOUR CLINICAL TRIAL DESIGN FROM GOOD TO GREAT.

Provided by:

McDougall Scientific
INSIGHTS YOU CAN TRUST

Study start-up is a stressful time.

Investors, executives, and trialists push to reach the first milestone of recruiting patient ONE, this makes it easy to miss opportunities to reduce recruitment requirements or study duration through careful planning. It is important to not rush the study start-up process and to ensure your study is primed for efficiency and precision. In this guide you will find recommended study design features that can help improve your clinical trials and likely save you time, money, and reduce risks to patients.

Contents.

Recommendations

There are a total of eleven recommendations that when applied will help take your trial from good to great.

The first five, are vital. The subsequent six are strongly recommended. We begin with those that are vital.

INCLUDE A STATISTICIAN ON YOUR STUDY DESIGN TEAM AND INCLUDE THEM EARLY.

Competition to develop therapeutic drugs and devices is fierce. At the same time, regulatory control, and the ability to recruit study participants creates challenges to maintain funding year over year. To reduce time and funding requirements and to maximize the information provided by study participants during the clinical phases of development, take a fresh look at the teams of professionals you employ and how you use them.

Statisticians, for one, can play a key role in efforts to enhance, optimize, and re-engineer processes and operations.

Like your scientific subject matter experts, your key opinion leaders, and your regulatory agent, a statistician is a vital member of the study design team. The statistician's job is to provide you with efficient design alternatives that answer your research questions with high confidence while adhering to regulatory requirements and business constraints.

Do not delegate statistical responsibilities to other SMEs or KOLs; they will not be familiar with innovative design features in the modern statistical toolbox.

Keys to having a Statistician involved early.

A

Before Protocol is Finalized

Have statisticians be involved early while the protocol is still under development. If statisticians are contacted only after the protocol is finalized, or worse, after the first patient has been recruited, then the opportunity for an innovative design is lost. Partnering with a qualified statistician early will expedite the product development lifecycle.

B

Statisticians as part of the team

Include statisticians in discussions with regulatory strategists, business decision-makers, and key opinion leaders.

information each role provides contributes to the design options and decisions.

C

Share concerns with Statisticians

Ensure that concerns voiced by regulatory authorities and stakeholders are provided to the statisticians.
This information guides them to present only the options that are acceptable to stakeholders and address key concerns.

D

Don’t rush the planning phase

Allow your design team enough time to gather requirements, assess available information, analyze existing study data, and simulate possible outcomes. Weeks spent during planning can shave months off study timelines and tens of thousands of dollars off budgets.

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CLEARLY STATE YOUR RESEARCH QUESTIONS

The typical flow of clinical trial data begins with the patient and ends with a clinical study report or publication. In between, data passes through a number of steps from collection to verification to analysis. Most stakeholders in clinical research view studies using this workflow and talk about milestones such as first-patient-first-visit, last-patient-last-visit, database lock, and first and final drafts of a clinical study report. Progress and performance metrics and, sometimes funding, are tied to these milestones.

Alternatively, statisticians design studies by considering the flow in reverse order. The first consideration is the research question; What questions must be answered by the study? You need to know what questions are to be answered by your study to design the study properly. The best approach to formulating the research question or objective is to write down the *answer* to the question. That is, what would you like to write in a study report?

Typical workflow:

Statisticians design studies in reverse order:

Envision that you are at the end of the study; write down the statement you want to appear in the clinical study report or a manuscript. Think about how you want your study to be cited by others. Your objective should describe the population, indication, endpoint, and clinically meaningful result. The statistician will then know what analyses are needed and what data are needed to support the analyses. Only then should sample size be determined.

Too often sample size is set first and everything else is fudged to "justify" that sample size; this is a recipe for failure.

Although stakeholders often like to jump immediately to the sample size question, doing so without due consideration of the previous steps risks making decisions with faulty information. Studies have been conducted, putting patients at significant risk and at high cost to funders, that fail to answer the research questions or meet regulatory requirements. Sample size requirements should only be determined once the iterations of the preceding steps have settled on appropriate study objectives, with supportive data, analysis, and design, to which all stakeholders agree.

> "The statistician's role is to ensure that research questions will be answered with a high degree of confidence while satisfying regulatory requirements, subject to business constraints and limiting patients' exposure to risk."

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REVIEW PUBLISHED STUDIES TO LEARN WHAT WORKED

Published literature can inform your study designers about endpoints, populations, confounding factors, and ethics committee and regulatory acceptance of design attributes. Conduct a comprehensive review of literature to learn about study designs and results in your therapeutic area or indication. Depending on how information from the review will be used, you might want to take the time to write a literature review plan to incorporate principles from the *Cochrane Handbook*. Writing a plan for a review team to follow is the best way to ensure unbiased selection of published, and perhaps unpublished, articles or databases, resulting in reliable information for you.

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REVIEW REGULATORY GUIDANCE TO LEARN REGULATORY REQUIREMENTS

Regulatory guidance documents will inform your study design team about acceptable design features like outcomes, endpoints, analyses, eligibility criteria, measurements, and more. This is **vital** if you intend to submit your product to a regulatory authority for market access but is useful for all study designs in general. Do not limit your review to the regulatory authority to which you intend to submit. Rather, search for guidance from other RAs because another authority might be on the leading edge.

USE A SEAMLESS DESIGN TO REDUCE TIME BETWEEN PHASES

Study start-up costs are usually high. You can reduce those costs using seamless designs that are intended to smoothly transition from one study phase to the next with only brief downtime. Phase I/II and II/III designs are common, but I/II/III designs have also been used. Seamless designs work well when you expect the later phase design to closely match the earlier phase with respect to major design features like the target population and primary endpoint. Write your protocol to include a decision between the two phases that allows you to not proceed to the next phase if you learn something in the earlier phase that would cause you to not want to proceed immediately. Examples of information that may lead to such a decision include safety concerns and a clear lack of efficacy.

6

BUILD MID-STUDY ADAPTATIONS TO INCREASE CHANCE OF SUCCESS

There are often many uncertainties about assumptions or requirements at the start of the study. Adaptations specified in the design can mitigate the risk of running an entire study on faulty assumptions.

Adaptive-By-Design means that the study protocol specifies permissible changes during the study's execution. A common adaptation is to re-estimate the sample size partway through recruitment. Almost any aspect of a study can be adapted, including the primary endpoint, eligibility criteria, treatment arms, and randomization methods. Decision criteria and relative time points should be specified in the protocol. Retrofitting an adaptation after the study has started causes avoidable costs in time and money.

Trials miss enrollment targets

Delay in clinical trials

Endpoints in trials have doubled

Clinical data collected in unstructured data sources

Source: QVIA Solutions

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USE EXISTING DATA *OR* EXPERTISE TO GREATEST EXTENT POSSIBLE

Data related to your study objectives might already exist and might have multiple sources, including earlier clinical studies, pre-clinical studies, studies conducted by other organizations, published literature, or even subject matter expertise.

These data may contain a wealth of information and should be thoroughly considered. Often, prior information is under-used by limiting its impact to sample size estimations. However, modern innovative designs make better use of existing data or subject matter expertise (if there are no existing data) through Bayesian methods or design features like synthetic control arms which result in lower recruitment requirements.

“modern innovative designs make better use of existing data or subject matter expertise.”

SATISFY ALL REGULATORY REQUESTS WITH DESIGN FEATURES

Regulatory authorities will not dictate a study design, but they will clearly state their concerns about a proposed design and will probably guide you about how to address their concerns. Ignore their concerns and guidance at your own peril. Submissions have failed because RA concerns stated during the design review were never addressed. Share correspondence from regulatory authorities with your design statistician so they see the RA's feedback and can address and incorporate it using appropriate design features.

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SIMULATE YOUR STUDY TO LEARN WHAT IS LIKELY

Hurricane centers simulate a hurricane's path using past hurricane behavior and weather conditions. They incorporate uncertainty of the weather conditions to estimate the probability that the hurricane will follow a given path.

Study design statisticians can perform the same exercise for your study. Simulations incorporate uncertainties that naturally exist to provide probabilities of realizing results of interest or even estimate how long a study will take to execute; information that is critical to making sound decisions.

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PLAN INTERIM ANALYSES TO STOP EARLY WHEN APPROPRIATE

Phase 1 and 2 studies are intended for learning. To save research funds and prevent study participants from being exposed to unsafe or ineffective treatments, design your early phase studies with "off-ramps". Consider incorporating interim analyses designed to detect futility. Contrary to popular belief, properly designed interim futility analyses do not have to incur penalties for hypothesis testing.

A common cliché in clinical research, "if you are going to fail, fail early", is meaningful advice for study design. **Failure in a study does not necessarily mean failure in product development**. Thorough analyses of the data from the failed study can uncover new knowledge that supports continued research.

In large confirmatory phase 3 studies, interim analyses for efficacy (which *do* incur penalties for the final analysis) are sometimes used to allow submission to an RA sooner than if the study had to run its entire duration. If you think your phase 3 might succeed early, it is wise to allow for an interim analysis for efficacy by writing it into your protocol. Before the study begins, build in flexibility to decide against the interim so you are not committed to stop the trial early if you decide you want more information.

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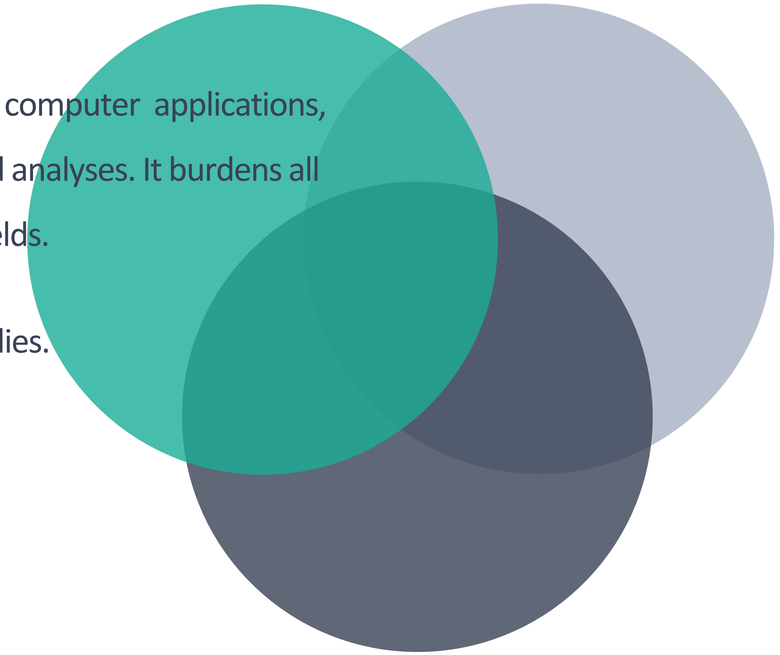
COLLECT ONLY THE DATA YOU NEED; NO MORE, NO LESS

Keep your eye on your target, which, in clinical phase development, is getting your product to market. Resist the temptation to gather “nice to have” information.

Adding unnecessary data collection increases costs for computer applications, site activities, and data cleansing, transformations, and analyses. It burdens all data handlers and may cloud focus on the vital data fields.

The “nice to have” items can wait for post-market studies.



Checklist.

Take your Clinical Trial Design From Good To Great.

ABSOLUTELY VITAL

- [ ] Include a statistician on your study design team
- [ ] Clearly state your research questions
- [ ] Review published studies
- [ ] Review regulatory guidance
- [ ] Satisfy all regulatory requests with design features

STRONGLY RECOMMENDED

- [ ] Consider seamless designs
- [ ] Include adaptations mid study
- [ ] Use existing data to the greatest extent possible
- [ ] Simulate your study using statistical models
- [ ] Consider interim analyses
- [ ] Collect only the data you need; no more, no less

IN CONCULSION

Assemble your design team to include **all subject matter experts, including a knowledgeable statistician.** Allow your team the time necessary to check all the boxes, from literature review to simulating your study results.

In doing so, you will be well-prepared and confident that no stone has been left unturned to implement a great study design. When a situation arises during the study, you are far less likely to be surprised because you will have discussed the possibility during the design process.

Careful planning and the application of these recommendations ensure that you not miss opportunities to reduce recruitment requirements or study duration and prime your study for efficiency and precision. The recommended study design features you found in this guide can help improve your clinical trials and likely save you time, money, and reduce risks to patients.

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Contact McDougall Scientific for a review of your Trial Design:

www.mcdougallscientific.com/request-information

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