Successful Studies Start At Feasibility

Study failure is every sponsor's biggest nightmare, and there are multiple reasons why it could happen. These may include a failure to properly recruit the correct study patients, missing study-critical data, or the drug not demonstrating the anticipated efficacy. Although there are few solutions when the drug does not exhibit its predicted efficacy, other risks to failure can be minimised or avoided by carefully identifying the study's potential pitfalls when planning it. This planning must start at the feasibility assessment stage, where the study is reviewed from multiple angles by the different cross-functional stakeholders. This process ensures that the investment made to conduct the study has the best opportunity of producing the reliable and reproducible data required for further development decisions and market registration.

Country and Site Choice

Feasibility usually starts prior to the study being awarded to the contractor by the sponsor, and typically, significant emphasis is placed on the identification of the region and countries where the study can be best conducted and on the estimation of the recruitment rate. The choice of regions and countries is in part driven by access to the required trial population, which in itself is determined by the prevalence of the indication, and also by the accessibility of medical treatments covered by private insurance or government-subsidised healthcare. Pre-existing treatments for the target indication can create competition for enrolment of patients; thus, the challenge for investigators who strongly believe in a new drug is to inspire their patients to participate in the study, despite the currently available standard of care regimens.

Additionally, the importance of the availability of well-organised study sites in chosen regions and countries should not be underestimated, as paradoxically, countries with a high prevalence of the disease, but only with access in the main to poorly-organised sites with limited or no coordination of services, will have challenges recruiting subjects even in seemingly-straightforward studies. Conversely, well-structured sites with dedicated recruitment staff offer the necessary connections with specialists and patient identification methods, even where a lower prevalence of the target population is evidenced.

Countries where trials in the same or similar indications have previously taken place are often well-suited to be shortlisted, as it implies that sites are available in those countries which have the necessary experience in recruiting the required population. However, the impact of potentially competitive studies seeking to recruit from the same patient pools also needs to be factored in, since such studies may substantially reduce the number of available sites that can adequately recruit in a timely manner.

Following on from country and site investigation, recruitment rates are the second critical parameter in the feasibility evaluation. Past experience is a good indicator of what will happen in the future – 'the best predictor of future performance is past performance' (Paul Meehl), provided that the context is similar. Therefore, benchmarking an upcoming study to similar - ideally identical – studies is an essential exercise in the enrolment rate evaluation.

Study Specifications - Recruitment and Retention

During this benchmarking exercise, a number of study specifications should be considered that may potentially affect recruitment rates. These may include the inclusion and exclusion criteria, prohibited medications, stipulated (invasive) procedures, the compound's or device's mechanism of action, the route of administration, and the burden for sites and patients. Engaging with one or more clinical specialists in the field may also add significant value in this assessment, as will feedback from sites on their experiences in similar studies in setting expectations. This becomes especially important at the final site selection step where each site's commitment must be considered individually in light of their previous recruitment performance, and how this may translate to the new study.

Overall study timelines can be developed from extrapolating the anticipated country/site distribution and recruitment rate analysis. The study's operational team can subsequently translate the feasibility parameters into a logistics execution plan to ensure targets are met.

As for recruitment, four significant barriers are acknowledged and must be adjusted for:

- subject-related (how the subject's perspective may impact their desire to enter the study);
- investigator-related (confidence in and motivation to conduct the study);
- protocol-related (design aspects which create complications);
- serendipity (a fourth, miscellaneous category which serves as a catch-all, for example, a delayed or extensive approval timeline).

To identify items in each of the categories along with proactive mitigation measures, stakeholders from the applicable functional areas participate in brainstorming sessions. This core team reconvenes routinely during recruitment to re-evaluate the barriers and approaches against the overall progress.

Similarly, the retention of subjects needs to be addressed early in the process and evaluated on an ongoing basis throughout the study until the last patient's final visit occurs. This is an area frequently overlooked by study teams, as the majority of sponsors place a primary focus on enrolment timelines; however, executing a study successfully goes far beyond merely enrolling the study as expected.

Achieving High-quality Study Results Requires Meaningful Data

Simply completing the enrolment portion is not what ultimately ensures confidence in the data following analysis; it is the quality of the data collected throughout the study for all those enrolled that will eventually drive the merit of the analysis. Efforts that

focus on optimising operational performance are required to deliver high-quality study results. In this, it is imperative to evaluate how the study's endpoints, and in particular, primary and main secondary endpoints, can be protected.

Endpoints may be objective (e.g. plasma viral load); subjective (e.g. quality of life questionnaire); or a combination of both (e.g. lung function spirometry tests where the participant and operator need to be properly trained and be familiar with the process to gain optimal results). Each one has its own critical nature and it is essential to start evaluating and discussing management and mitigations early on in the process with all stakeholders involved, including vendors. A good example is where the feasibility team may suggest the use of an electronic clinical outcome assessment (eCOA) device to capture a specific endpoint. If paper back-ups are requested by the sponsor, this not only implies development, printing and shipment of the paper back-up, but also the need to identify upfront who will be responsible for the data transfer into the database. This may be the study site, eCOA vendor or data management vendor, but each may impact the risks, resources, timelines and cost to the study in a different manner.

Ensuring that a study has the greatest chance of success starts well ahead of the commencement of the clinical trial itself. It begins with meticulous planning and undertaking robust feasibility assessments at an early stage with a multidisciplinary team comprising experienced, knowledgeable and forthcoming stakeholders, who drive the project, and are willing to assess and plan for each potential eventuality.

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