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Operational Input from Investigators for Protocol Feasibility Assessment

By Lisa Palladino Kim, Otis Johnson, and Brendan O'Neill

Scientific and regulatory needs drive the design of many protocols, often resulting in trials that are larger and more complex than necessary.[1] Just as input from key opinion leaders can provide valuable input on the science of a study, input from proven investigators can provide valuable input on its execution. Obtaining this input during the protocol design stage on aspects like eligibility criteria, treatment guidelines, procedures, epidemiology and competitive landscape can help create simpler, more practical designs. Engaging experienced investigators early in the process can also foster collaborative relationships that can be leveraged throughout the life cycle of a development program.

By creating a network of investigators — consultants — that have experience conducting trials in a particular disease area, a pharmaceutical company can create a valuable resource that is available on short notice in a standardized protocol design process. Before recruiting investigators for your network, review your clinical development plans and existing internal and external resources to identify anticipated challenges, e.g., studying a new population, and gaps in its knowledge, e.g., standard of care in a geographic region.

There are numerous ways to engage the network, ranging from one-on-one telephone conversations to online questionnaires to face-to-face group meetings. The optimal methods and timing depend on the specific needs of the company and how it prefers to work with consultants. Factors to consider include the nature of the issues to address, the time and budget available, the geographic locations and availability of the consultants, and the degree of interaction among consultants.

As with any consultant, it is important to define the objectives — in this case, the questions to be answered — as clearly as possible. Some questions might be very specific, for example: "What type of physician typically sees patients with the medical condition in question?" Other questions might be very general, for example: "What other challenges do you anticipate in your country?"

Questions typically cover at least the following areas:

- Incidence or prevalence of the medical condition
- Access to potential study subjects and suitability of eligibility criteria
- Acceptability and logistics of study procedures for healthcare providers and study subjects
- Standard of care and compatibility with treatment guidelines
- Use of placebo or choice of comparator drug and its dosage

Focus on the questions that are likely to make a significant difference, based on their potential impact on the study and your level of uncertainly about them. For example, if you suspect that the protocol requirements may be too burdensome for study subjects, ask questions about their tolerance of study procedures. However, do not limit your questions so much that the consultants do not point out issues that have not already occurred to you. It is not necessary to ask every consultant all the questions.

Multiple consultants are likely to give answers that conflict, so interpret the responses based on level of agreement, as well as the respective background, perspective and expertise of

each consultant. By establishing ongoing relationships with a network of consultants, you can better interpret and weigh their advice for a specific study.

Compile and summarize the feedback in a coherent report, obtaining clarification where appropriate, organized by functional area. Within each area, some findings will be definite, e.g., all the consultants might agree that a study visit needs to be divided into two visits. Make recommendations in the report based on definite findings. Other issues might be unresolved, e.g., the optimal dosage of the comparator drug. It is also common for new issues to emerge that need to be resolved through internal discussion or follow-up with one or more consultants. Clearly define the status of the open issues and create a plan to expeditiously resolve them, decide if and how the protocol should change, and then how to implement the changes.

In addition to possible revisions to the protocol, the report might also influence other deliverables and processes, such as defining the characteristics of appropriate research sites or adjusting subject recruitment and retention strategies.

As the following examples illustrate, network input can help the study team justify its conclusions in discussions with protocol authors, management and regulatory authorities.

Example One

A study team was concerned that it would be difficult to enroll and retain subjects in a study that required three invasive procedures. The team therefore asked the investigator network for input on the issue. The network estimated that only 10-20% of patients would participate if three invasive procedures were required, but 60-100% of patients would accept at least one invasive procedure in the study. Based on this feedback, the study team asked the protocol authors to reconsider the design. After review, the authors agreed that a design with only one invasive study would still achieve the scientific objectives. In this case, the authors, fortunately, were able to change the study design. However, if the change had not been possible, the network's input would have given the study team a firm basis to extend the enrollment period and add resources to deal with the retention challenge.

Example Two

The European Union Pediatric Development Committee requested design changes to a planned protocol concept that would make a study extremely difficult to implement. Feedback from pediatric consultants in Europe confirmed the difficulties and helped support a compromise with the Committee on study design.

Conclusion

Successful studies achieve scientific, regulatory and operational objectives. Just as a network of key opinion leaders is a valuable resource for the scientific aspects of a protocol, a network of proven investigators is a valuable resource for the operational aspects. To be effective, an investigator network must consist of the right people, be asked the right questions, and be given credence in operational protocol issues.

Reference

1. Mullins, D., Whicher, D., Reese, E., & Tunis, S. (2010). Generating evidence for comparative effectiveness research using more pragmatic randomized controlled trials. *PharmacoEconomics,* 28 (10), 969-976.

Authors

Lisa Palladino Kim is a Global Trial Optimization Specialist at PharmaNet/I3, dedicated to Merck. Contact her at 1.267.305.5943 or lisa_palladino@merck.com.

Otis Johnson is an Associate Director of Clinical Research at Merck. Contact him at 1.732.594.8611 or otis_johnson@merck.com.

Brendan O'Neill is a Director of Clinical Research at Merck. Contact him at 1.267.305.7954 or bendan_oneill@merck.com.

