Efficient Beginnings

Designing and executing large-scale global clinical trials can be challenging. Careful consideration of timelines, regulations and enrolment, including comprehensive risk and contingency plans, can help to ease the process

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Commencing a large global clinical trial and completing patient enrolment on time are often the most challenging aspects of study execution. Aggressive project timelines, resource fluctuations and diverse regulatory environments increase complexity and place pressure on project teams as they work to provide deliverables and achieve trial milestones. It is this start-up phase, including patient enrolment, which is particularly critical to completing the study successfully.

This article will discuss effective risk management and planning techniques for rapid study start-up, communication plans, managing regulatory submissions and interactions, monitoring plans, and applying strategic resources to critical tasks that can ensure the successful conduct of a large global clinical study.

Risk and Contingency Planning

A critical component of managing clinical trials is risk management and contingency planning. Effective risk management and contingency plans must be actively maintained, reviewed and revised as appropriate during the trials. This approach to risk mitigation needs to be applied to the various aspects of clinical trials.

Realistic Enrolment Target

Determining realistic enrolment rates can be challenging, and study teams often don't get it right. Traditionally, study teams use historic data, feasibility questionnaires, modelling tools, prescribing information or disease prevalence to identify the best principal investigators (PIs). Sophisticated predicative tools can be used but they do not guarantee success; it is important to factor in contingencies such as additional countries and PIs to ensure enrolment goals will be met when the unexpected happens.

Communication Plans

A detailed communication plan is recommended to manage and coordinate large global study teams working with multiple vendors and global affiliates. Although communication plans are routine in all clinical trials, they are especially important for large global trials due to the number of stakeholders participating, including sponsor, CRO, vendor, investigator personnel, and so on. Time spent in preparing a comprehensive communication plan increases the likelihood that all parties are aware of, and are working toward, achieving the key study goals.

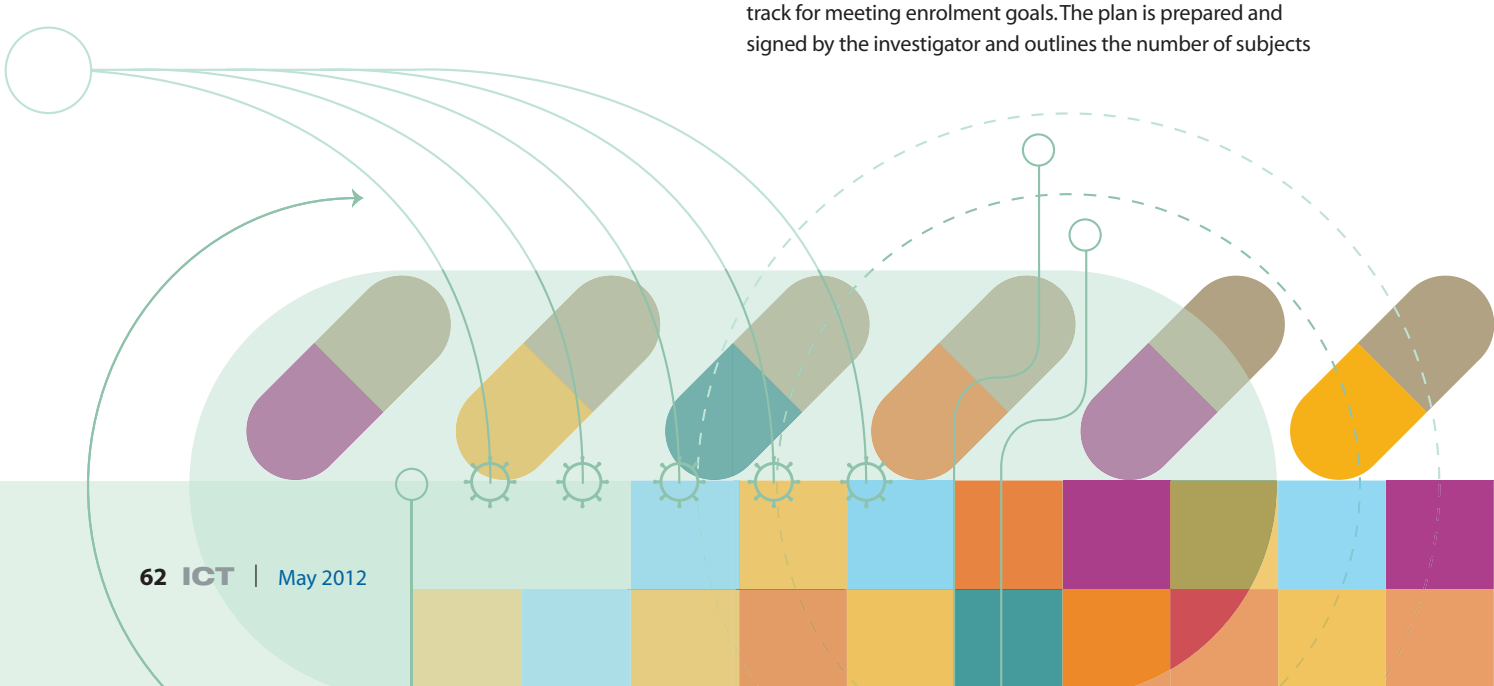
Site Selection

Once a study team determines the number of sites and countries that will be needed, experienced sites compliant with Good Clinical Practice/International Conference of Harmonisation (GCP/ICH) and local guidelines must be identified. The best sites must be able to identify, screen and enrol qualified subjects quickly. For longer term studies, staff and subject retention is critical and should be factored into the site selection. A process for patient retention should be implemented immediately.

When selecting appropriate sites, study teams can use site lists from previous studies and search available databases. Depending on the indication, teams can also recruit sites new to clinical trials. Several tools can be used to help identify the best sites in addition to a protocol-specific site selection questionnaire. Unique site grading tools can be considered for clinical studies where the protocol provides clear requirements that can be measured to assist in selecting the right sites.

Meeting Enrolment Goals

Once sites have been selected an investigator recruitment plan can be utilised by study teams to ensure that each site is on track for meeting enrolment goals. The plan is prepared and signed by the investigator and outlines the number of subjects



the investigator plans to screen. It includes the tools and the process for how the site plans to identify patients for screening and, ultimately, how the investigator will meet the recruitment goal. The investigator recruitment plan is beneficial, as the investigator has accountability for meeting his/her recruitment goals. This document provides the sponsor or CRO with a platform to support site recruitment efforts and determine any additional tools or processes that could be applied quickly, as needed. Additional motivation for patients and site staff can be provided by the study staff through frequent contact, newsletters, and an appreciation programme. Study-specific appreciation programmes should be conducted in accordance with all PhRMA Guidelines and with institutional review board/ethics committee (IRB/EC) approval as required (1).

If selected sites are not able to screen effectively in a short time period, and additional support for the site is not effective, it is recommended that the site be closed. This can minimise the number of non-performing or low-enrolling sites and allows resources to focus where there is a higher likelihood of meeting enrolment.

Regulatory Challenges

With any protocol it is always possible that competent authorities (CA), institutional review boards (IRB) or ethics committees (EC) will request protocol changes or additional information during the review and approval process. Identification of a sub-team to focus on responses and feedback from regulatory bodies will help ensure teams meet the timelines required for a response. During critical time periods, weekly meetings can be scheduled. Detailed tracking spreadsheets are also beneficial in ensuring that study teams are able to respond quickly and efficiently to CA and EC questions.

Strategic Study Support

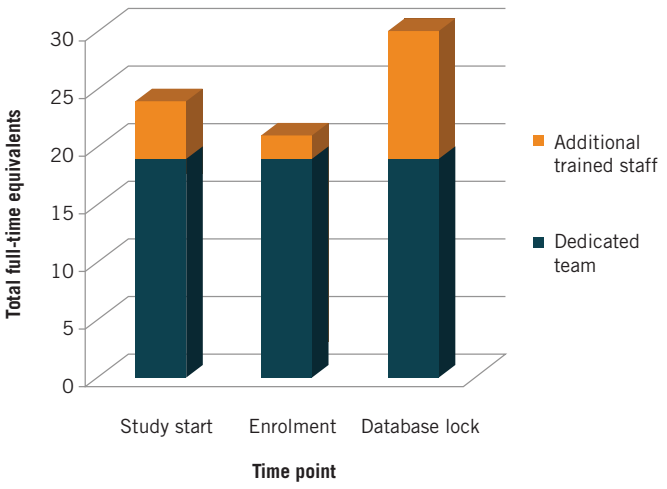
Another effective management practice in large trials includes adding non-dedicated support to assist fully assigned team members during critical phases. Having highly trained strategic resources available during peak periods enables the study teams to achieve study start-up and recruitment goals. Figure 1 demonstrates a strategy for the application of these strategic resources applied to a hypothetical, large global clinical trial.

A Discussion about Monitoring

For the monitoring phase, study teams should develop detailed plans which outline processes and frequency for monitoring visits. Most studies have used 100 per cent source data verification (SDV) and frequent on-site visits. Some studies set triggers for monitoring visit frequency and duration based on patient enrolment for each site or utilise a reduced SDV focusing on key efficacy and safety parameters. This aspect can be challenging for CRAs to implement, especially those who used the 100 per cent SDV model of monitoring.

With the new Draft Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring released

Figure 1: Critical time point resourcing strategy



August 2010 by the US Food and Drug Administration, the traditional monitoring every four to eight weeks with 100 per cent SDV on site is being looked at differently. As individual companies set their plans for risk-based monitoring, it may be worthwhile to compare future studies employing a risk-based approach with historic trials run using a standard monitoring plan in regard to data quality, safety, and monitoring costs.

Conclusion

Although every clinical trial presents its own unique challenges, a few key elements stand out as recommended for all clinical trials. The development of comprehensive risk and contingency plans and communication plans is essential. Inclusion of additional countries and sites is highly recommended for global trials to help ensure adherence to overall patient recruitment timelines. Strategic support to study teams during the start-up period can also help ensure success. Finally, it is critical that sponsors and CROs bring the right resources and the right tools and techniques to the clinical trial start-up process to meet study start-up and enrolment timelines.

Reference

1. **PhRMA Code On Interactions with Healthcare Professionals, 1 July, 2001**

About the author

Kellie Malloy is Vice President of Pain and Inflammatory Disease/Cardiovascular and Metabolic at PharmaNet/i3. She has over 20 years of experience in the management and oversight of clinical trials. Prior to joining PharmaNet/i3, Kellie held several clinical research positions. Her experience includes over 80 clinical trials in adult and paediatric patient populations, relating especially to cardiac, inflammatory, metabolic and pain indications. Kellie has a BSc degree from St Joseph's University in Philadelphia, PA.

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