

Metrics and Trial Management

Richard Walovitch and Asli Memisoglu of WorldCare Clinical discuss how working with an imaging CRO can increase your chances of success

The use of medical imaging in clinical trials has increased considerably in the last decade as imaging biomarkers are more frequently accepted as surrogate endpoints in oncology, cardiology and neurology trials. But this short history means that navigating the imaging section of the study process remains unfamiliar to most sponsors, and imaging CROs must be able to step in at the outset to define responsibilities and set expectations through clear communication with sites and sponsors. Everything from worldwide site qualification and training to imaging charter and protocol development drive contract and study start-up deliverables, and managing these early steps efficiently – and tracking their effect – is critical to setting the stage for the trial's success.

Currently, efforts to complete this 'tracking' are underdeveloped and incomplete. Most trials employing imaging are run as a mix of manual paperwork and automation, and the need for a comprehensive digital solution is growing by the minute. In order to maximise efficiency in international trials, CROs must be engaged at the trial's start and should be fully employed – and at the reins – until its end.

As sponsors become more experienced in outsourcing this trial expertise to imaging CROs, their ability to implement metrics to evaluate performance and increase efficiency over the duration of the entire trial will become easier. If one partner is engaged from inception until submission, successfully measuring performance throughout is a practical possibility –

and should be a paramount aim. The US-based Metrics Champion Consortium (MCC), a non-profit organisation made up of biotechnology, pharmaceutical and service provider organisations, is currently the seat of a centralised industry effort to develop, through collaboration, the appropriate metrics to realise this goal. Through several different working groups for clinical trials, central labs, ECG and imaging, the MCC is working to encourage performance improvement and appropriate levels of cooperation and control for sponsors and CROs in support of the drug development process. The only way to truly succeed at the metrics game, however, is to recognise and manage the full role of the imaging CRO.

BRINGING IN THE CRO

When beginning an imaging trial, sponsors should partner with the imaging CRO as early as possible. Establishing the relationship at the beginning, before set-up and site qualification, helps to ensure a more efficient trial management process and helps to define duties clearly for both parties. Sponsors that engage CROs at a later stage in the trial may not only confuse this allocation of responsibilities, but also are not taking full advantage of the very expertise for

which they have paid. Imaging trial design and management can often be overwhelming to sponsors, and even for those more familiar with the process, underestimating the challenges unique to an imaging study is common. The use of multiple sophisticated modalities creates a complex workflow, and increases the importance of technical acumen in the science of imaging as well as the operational details of workflow management.

Any CRO brought on board should therefore be involved from the very beginning in order to ensure these aspects are considered during the contractual process. Maximising this special experience ensures all data collected is viable for regulatory submission. For global trials in particular, the imaging CRO's niche expertise in developing study protocol, the imaging charter, and the imaging acquisition guidelines are critical to shaping a trial design that adheres to international compliance standards and regulations.

In parallel, early planning is also critical to the successful implementation of metrics and requires consensus and/or standardisation between the CRO and sponsor even prior to protocol development. The MCC's recent release of its standardised Imaging Metrics (version 1.0) forms the framework for potential standardisation beyond one-to-one contract research relationships, and may well prove to be a valuable starting point for nailing down industry-wide accepted metrics on which all sponsors and CROs agree.

Because operational metrics are levied even before the trial begins (imaging budget variance and contract signature time are good examples), early communication is required. Prior to initial protocol development, CROs must confirm the metrics to be used with the sponsor. Moreover, since image acquisition, processing and quality metrics are integral to workflow comparisons and post-study evaluation, sponsors must recognise and accept the standards of measurement to be used by the CRO. Without a current industry-wide standard, the entire trial depends on mutual agreement between both parties, or otherwise any measurement is meaningless.

IMAGING CHARTER AND ACQUISITION PROTOCOL DESIGN

Specifically, CROs can minimise variances across global sites and facilitate a smoother trial by joining the protocol development stage as early in the process as possible. Standardising the Independent Imaging Review Charter (more simply known as the imaging charter) and image acquisition protocol design before any site qualification or patient participation begins dramatically reduces the variability in image acquisition across global sites, and improves performance characteristics for maximum efficiency (and regulatory-ready data).

The imaging charter provides details of how reading interpretations will be executed with the central reviewers, documents how the reader(s) will be qualified and trained, and delineates the response criteria to be used. The charter serves



as the official record of the central reading processes, and it is recommended that it is submitted to the appropriate regulatory body for approval prior to the start of any central reads.

Accordingly, the imaging CRO should work closely with the sponsor to provide guidance in designing the imaging charter. Sponsors should also put the CRO in charge of the image acquisition protocol, which is usually part of an image preparation and submission guide developed before the study begins. This document provides the study-specific details for image capture, such as a complete description of imaging parameters, appropriate instrumentation, timeline, subject positioning, and so on. It also includes standardised instructions for clinical investigators and onsite imaging manuals for imaging technologists with information on the imaging procedure, equipment setup and format of radiological output. But no matter which party takes the lead, it is always the imaging CRO's responsibility to ensure that all final documents apply accepted standards of GCP guidelines, including defining, monitoring and auditing study methods, as well as analysis during and after the study.

QUALIFICATION, COORDINATION AND START-UP OF IMAGING SITES

In conjunction with document development and approval, the imaging CRO also assists the sponsor in locating and qualifying appropriate imaging sites. This includes remote or on-site preparation, such as a review of equipment variability and data transfer capabilities at participating facilities, hardware and software configuration if necessary, and specialised technical support for all sites.

Technologists at imaging sites should receive training to ensure that they fully understand the details of the acquisition protocol developed at the beginning of the trial. In addition, the CRO should present the image preparation and submission guidelines to site personnel, and instruct them on the processes for delivering all images and data to the imaging CRO and for archiving relevant images and data on-site.

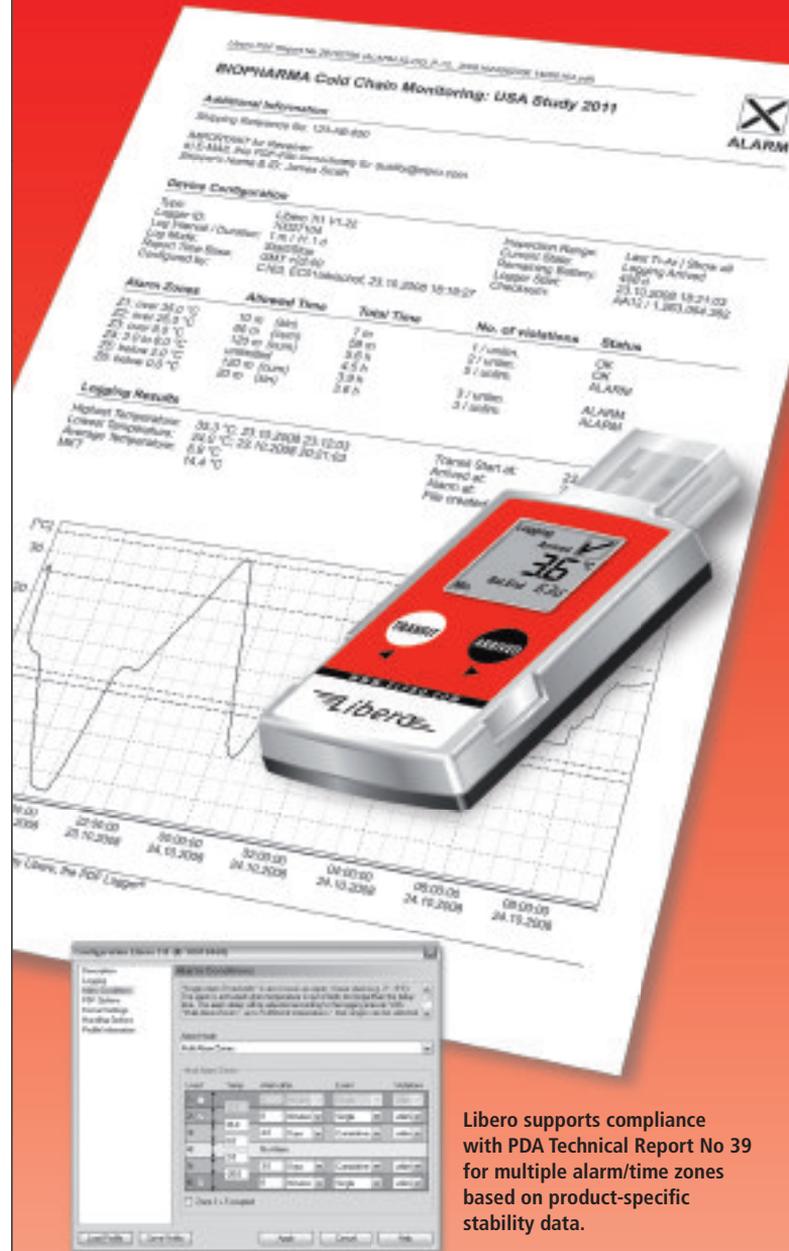
During this initial set-up, the CRO should also work with the sponsor to identify potential problem areas as early as possible. Site coordination and training efforts should continue throughout the trial, focussing on technical difficulties that may increase trial time or cost, to allow managers to make the appropriate adjustments to prevent them.

In addition, the CRO must ensure that image acquisition is managed according to protocol throughout the trial, and should continually provide feedback to sites to ensure that consistent, high-quality data is obtained. In order to reduce data variability and protect image quality, continual review and monitoring of the imaging sites over the duration of the trial is required as part of a rigorous and well-documented quality control process.

The implementation and regular tracking of metrics is also very important, as real-time evaluation can catch problems during the trial and allow for immediate readjustment. Such a

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proactive approach will increase savings over the total trial if remediation is addressed at the point of evaluation and the problem is solved before the trial is completed. By eliminating the need for retroactive efforts to reconcile the data or a partial re-run of facets of the trial affected, CROs can reassure sponsors of an on-time, on-budget study.

METRICS: A CLOSER LOOK

Excepting the exploratory measurements that address reader variability and are not yet part of the working group's official recommendations, the MCC's Imaging Performance Metrics v1.0 currently primarily consider operational statistics. This includes everything from site start-up performance (the average number of calendar days from the site designated ready to first date of image receipt) to measurements of image quality, processing and queries, although the most important are undoubtedly those that provide insight into the quality of the data. A record of the percentage of non-evaluable images, for example (those that were not acquired according to correct protocol or are visually unreadable for some reason), gives sponsors a means of assessing the quality and consistency of site performance and image acquisition over the course of the trial. Comparing a baseline number at the beginning of the trial with the percentages captured throughout the study offers warnings

of potential site problems to be addressed, and is helpful in evaluating trial efficiency and CRO performance at its end. Likewise, a record of the percentage of site queries can provide evidence of the quality of the images; if a number of queries are needed and the images' delivery to readers is delayed due to confusion, image quality may be an issue, and the resulting increased trial time always becomes a monetary concern. As the industry moves toward a standardised system of metrics, however, reader performance should indeed become a focal point. To ensure that the data acquired and analysed is both accurate and valid for regulatory submission, these metrics are already an internal necessity at imaging CROs.

Reader variability should be minimised as much as possible with the steps explained earlier during acquisition protocol design, as well as with uniform and comprehensive reader training. Training must focus on defining clinical terms and collectively testing performance before product reads are started. Metrics for measuring reader variability include those that describe the variability in the interpretation of a set of images across different readers (inter-reader variability), as well as those that describe variability in the interpretation of a set of images by the same reader at different times (intra-reader variability). While today's reader variability statistic standard for categorical endpoints is a simple percentage reader agreement, more robust metrics, such as the kappa statistic, exist and provide a means by which to measure variability more accurately by taking chance agreement into account. For continuous endpoints, concordance correlation coefficient endpoints are recommended. Armed with a valid measure of reader variability, the sponsor and CRO can investigate the causes of low reader reproducibility and proactively identify potential problem areas to be addressed. Factors such as insufficient reader training, low individual reader performance, unclear read criteria, poor image quality and others are common causes, but the efficient use of these statistics will enable both parties to take the appropriate remediation steps to increase the trial's chances of success.

In addition to this variability, read characteristics, such as interpretation duration and the time of day of read completion, can be monitored, and the potential impact on performance can be evaluated. It is particularly important for sponsors to work with a CRO that recognises the importance of these additional factors, and has the technology capabilities to capture and record them for real-time or future evaluation.

CONCLUSION

As the importance of operational and clinical metrics increases with time, global sponsors must work to engage those CROs with the appropriate internal metrics and outsourcing approach to handle a complex trial – and they must do so at the outset of the study. By standardising the implementation of metrics and working with the CRO from the very beginning to manage study set-up and initial documentation, sponsors can take full advantage of their specialised expertise, as well as their joint efforts to improve process and performance through comprehensive tracking and response.

About the authors



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