

Efficient and Cost-Effective Monitoring for Observational Studies



The success of new biopharmaceutical products no longer depends on simply obtaining approval from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) or other regulatory bodies. While such approvals allow companies to market their products, there is no guarantee that products will achieve acceptance in the global marketplace. Stakeholders such as reimbursement agencies, managed care organisations and patient-advocacy groups now demand more data than results obtained just from pre-approval clinical trials, which typically involve relatively small numbers of patients, are narrowly-focused by stringent eligibility criteria to ensure uniformity, and are evaluated by highly-trained research investigators. Today's new products must demonstrate efficacy in a controlled environment, and "effectiveness" in a real world setting that embraces patients having multiple co-morbidities being treated by physicians according to standard of care, rather than a rigid protocol developed by the product's manufacturer. Given the significant side-effects that have been demonstrated for several new products (albeit at a relatively low incidence), such effectiveness assessments also require many more patients than were evaluated for pre-approval clinical trials in order to assess the product's true safety profile.

The evolving drug development environment described above has ushered in an era in which observational studies -- including long-term registries, retrospective analyses and various approaches to collecting patient-reported outcomes -- are now widely employed to obtain critical information regarding the appropriate use of newly approved products. Such studies -- which are non-interventional in the sense that no study drug is administered -- seek to evaluate patients in a natural setting. As such, these studies typically employ few if any patient inclusion/exclusion criteria, involve no protocol-driven visit or sampling requirements, and are often conducted by physicians who have little or no experience with clinical research.

This latter study design element -- reliance on medical personnel with little resemblance to the investigational sites typically employed for randomised clinical trials (RCTs) -- creates obvious challenges. These include ensuring that physicians and their staff are adhering to even very modest requirements for observational study, and that data is collected and entered in a timely and credible manner. This article describes various approaches to monitoring the performance of sites participating in observational studies, as well as the advantages and limitations of each approach.

Monitoring Site Performance for Observational Studies -- Potential Options

The range of monitoring options for observational studies varies from the same intense approach used for RCTs, to dispensing with monitoring altogether. As will be seen, there is no approach that will work for every type of observational study. Each option must be considered within the context of the study's objective and the purpose for which the resulting data will be used.

Option No. 1 -- Intense On-Site Monitoring: The most effective method to monitor site performance for any clinical research study is the approach taken with RCTs, namely sending contract research associates (CRAs) to inspect the physicians and their staff at six- to eight-week intervals. The CRAs will then spend an entire day on-site scrutinising all aspects of patient enrolment and treatment, auditing study drug inventory and reconciliation logs, and evaluating procedures for data collection and case report form (CRF) completion. However, some registries can last ten years or more and may involve 20 or more countries and 1000 or more sites. Using such an approach is impractical as the travel costs for the inspectors alone would be millions of dollars. Employing an RCT-type monitoring approach is also unnecessary for observational studies. For example, the medications patients receive are all commercially available, eliminating the need to inventory and reconcile study drug logs. The wide use of electronic data capture (EDC) for observational studies also generally removes the need for CRF review.



Option No. 2 – Limited On-Site Monitoring: To address the cost of monitoring for lengthy observational studies, many sponsors simply choose to reduce the frequency of on-site visits from every six to eight weeks, to every six to twelve months. While such an approach certainly results in a more palatable budget, the lack of interaction with CRAs typically leads to a deterioration of site performance, both in terms of patient enrolment and data collection and entry. The reason is obvious: given their limited experience with clinical research, physicians and staff involved with observational studies need frequent contact to reinforce appropriate performance. Without repetitive contact they quickly revert to their routine behaviours.

Another approach is to eliminate monitoring completely and simply collect patient-related information electronically, or have sites submit data via fax or expedited delivery. This option is effective for observational studies in which retrospective information is simply collected from a managed care database. It is also widely employed for studies involving abstraction of information from medical charts, since inspectors are typically precluded from examining patient records due to privacy restrictions. However, such an approach for prospective observational studies has obvious limitations and would call into question not only the credibility of patient enrolment information, but also the data that was collected.

Option No. 3 – A Balanced Approach to Monitoring: An alternative to providing too much or too little monitoring is to engage with sites remotely via telephone. Such an approach is frequently confused with call centres, where individuals with a minimal amount of clinical training assist with patient recruitment, market access tracking and similar activities. In contrast, Remote Monitors for observational studies are experienced CRAs who play a critical role in managing day-to-day site performance. Much like an air traffic controller, who does not need to be physically in the cockpit of an airplane to know whether the plane and crew are performing as expected. Remote Monitors can ascertain whether sites are meeting expectations by checking indicators such as the time required to complete study start-up documents, the need for repeated training of study procedures and the amount and quality of data entered via electronic data capture (EDC) (to which the Remote Monitors typically have access). Remote monitoring obviously cannot be employed for source document verification and other tasks that require an on-site visit. However, frequent contact with sites via phone, even if only for a short period of time, is a very effective way to reinforce desired behaviours such as enrolling

patients, ensuring identification of all potential safety-related events and quickly triaging potential problems.

Figure 1 illustrates the variety of observational study tasks that can be successfully handled by a Remote Monitor managing their sites via phone.

Figure 2 is a standard approach to monitoring sites participating in a long-term observational study such as a registry, via a combination of monthly remote monitoring and annual on-site visits. The combined approach provides an effective means for ensuring that source documents, informed consent forms and regulatory documents can be audited (via yearly on-site visits) and that sites have ample opportunity to “bond” with their primary monitor via frequent interactions on the phone. The key to ensuring that the model works as designed is as follows: 1) the Remote Monitor must be an experienced

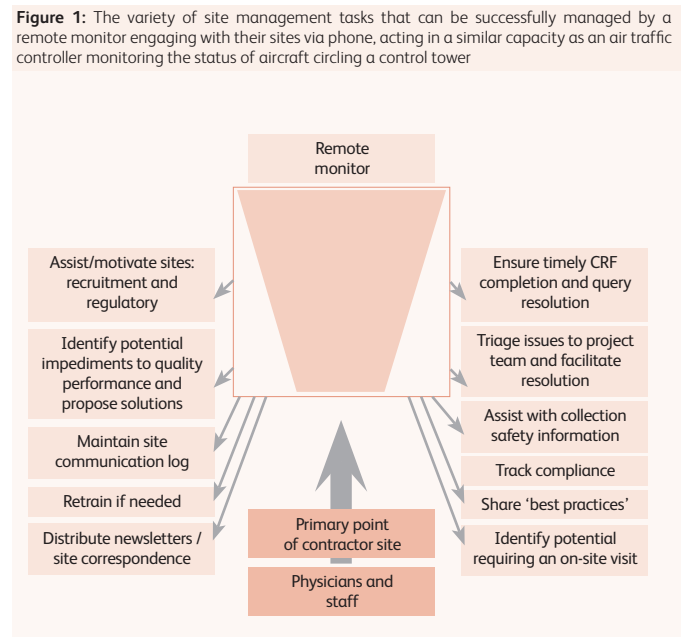
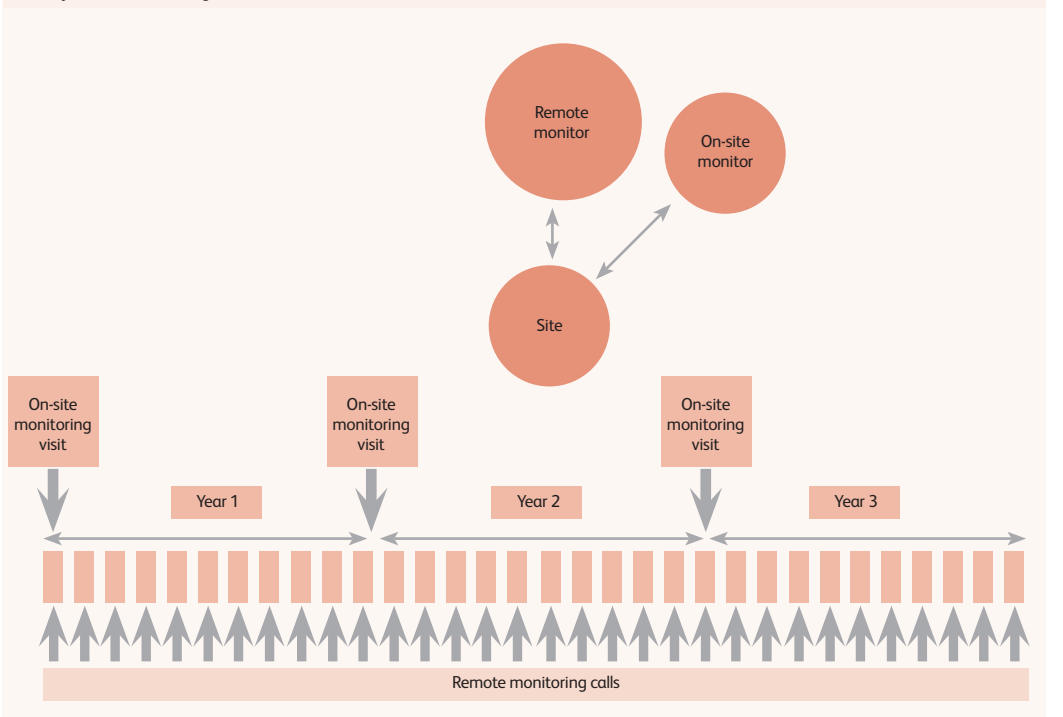


Figure 1: The variety of site management tasks that can be successfully managed by a remote monitor engaging with their sites via phone, acting in a similar capacity as an air traffic controller monitoring the status of aircraft circling a control tower

Figure 2: A standard approach to monitoring sites participating in a long-term observational study such as a registry, via a combination of monthly remote monitoring and annual on-site visits.



CRA who is adept at identifying early warning signs of potential problems; 2) an effective triage system must be established to ensure that appropriate actions can be taken in response to early warning signs; and 3) a “pool” of additional on-site monitoring visits should be included in the budget to make out-of-cycle visits to sites that may be experiencing difficulty meeting their study obligations. Typically this pool can be as small as an additional 10%, and is used on an as-needed basis for under- or over-performing sites, or for cause.

Although this approach appears to break the most important commandment of monitoring – that all sites have a single point of contact – that is not the case. For observational studies, the Remote Monitor is always designated as the site’s single point of contact, given the infrequency with which the on-site monitor visits the site.

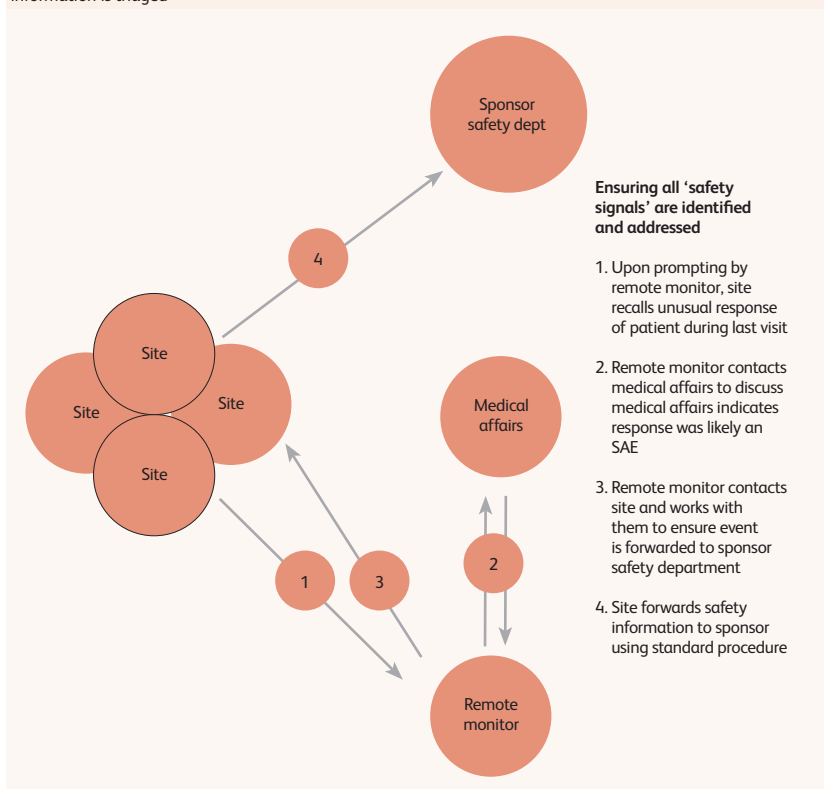
As mentioned before, one of the primary responsibilities for a Remote Monitor is triaging unexpected developments to identify potential problems quickly and achieve prompt resolution. One of the best examples of this responsibility is the early identification of possible safety-related events. Many observational studies are conducted to monitor the long-term occurrence of serious adverse events (SAEs) in the real world of standard clinical practice. However, despite the extensive training typically provided by sponsors regarding the importance of reporting potential SAEs, sites involved with observational studies often over- or under-report such events. This can be due to their lack of experience with clinical research, their unfamiliarity with products new to their practices, and/or their limited contact with the sponsor or monitor.

This challenge could be addressed by instituting a rigorous RCT-type approach to frequent on-site monitoring, or by using a full-time Medical Monitor to engage with sites and field questions from them. Both of these approaches are expensive and generally unnecessary. A better method is illustrated in Figure 3, which shows how frequent interactions between the Remote Monitor and sites can reveal information regarding “safety signals” that might not otherwise have been reported to the Sponsor’s Safety Department. In this example, the Remote Monitor uses probing questions to learn about an “episode” that may or may not have been an SAE, then discusses the episode with an appropriate physician in Medical Affairs to ascertain its potential importance. If the episode is deemed to be a potential SAE it is reported to the sponsor’s safety department for further review. The Remote Monitor then questions other sites regarding the occurrence of similar episodes and, if warranted, initiates supplemental training to ensure that this safety signal is being uniformly reported to the sponsor.

Conclusion

The growing importance of evaluating products in the real world has led to an increase in the conduct of registries and other types of observational studies and greater emphasis on the overall effectiveness and long term safety of new products. This has resulted in larger and lengthier post-approval studies.

Figure 3: An example of how frequent interactions between the Remote Monitor and sites can reveal information regarding “safety signals” that might not otherwise be reported to the Sponsor’s Safety Department, and how this information is triaged



These changing patterns have focused attention on the need to carefully evaluate the methods employed for monitoring observational studies. This ensures not only that costs are minimized, but also that the approaches employed yield reliable results that will satisfy all stakeholders involved, including regulators, reimbursement agencies, physicians and patients.

One such method is the use of frequent remote monitoring by an experienced CRA to provide sustained engagement with sites throughout the long duration of a registry. When appropriately staffed and managed, remote monitoring can provide an effective means to assess site performance, triage problems and maintain motivation. When linked with limited on-site visits to audit proper documentation of events and outcomes and the appropriate completion of regulatory documents, the combination provides an effective and cost-efficient approach for monitoring observational studies.



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