Risk Based Monitoring

Renewed focus on data-centric approach to managing clinical trials

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The outbreak and spread of the COVID-19 (SARS-CoV-2) pandemic continues to have a significant negative impact on the clinical trials industry. Restrictions to curb the spread of the virus caused many sites to be temporarily closed to external visits and resulted in postponements and delays to trials. In spite of these challenges, the industry has shown considerable resilience by rapidly deploying alternative strategies to keep clinical research projects on track. Establishing and effectively implementing these strategies continues to be essential not only to ensure the safety and well-being of patients and the continuity of vital clinical research, but also to preserve the integrity of the data generated from this research.

In this article Cromos Pharma's Chief Operating Officer Stephanie Finnegan explores the role of Risk Based Monitoring (RBM) in clinical trials, how it has been utilized in response to the pandemic, and how the experience may shape the industry's approach to RBM in the future.

Responding to the challenges around monitoring trials during the pandemic

One of the areas of clinical research most affected by the pandemic is that of on-site monitoring and verification of data. Clinical trial monitoring is a core element of human clinical research, aimed at protecting patient safety, ensuring data integrity and promoting protocol compliance. Clinical trials have traditionally relied on an on-site approach to monitoring and Source Data Verification (SDV), with on-site visits occurring every 6-8 weeks on average.

However, global measures aimed at reducing the spread of COVID-19 included almost immediate and simultaneous restrictions on the movement of people, with the result that site-based monitoring visits have not been a viable option for two-three months now. In fact, most geographic regions are still contemplating when and how to safely ease these restrictions. To respond to this challenge, the industry has employed alternative monitoring methodologies that are not conducted on-site but are centralized and remote.

How can we use Risk Based Monitoring to maintain trial and data integrity?

The immediate switch to entirely remote monitoring and the unavailability of traditional SDV raised legitimate concerns throughout the industry regarding the overall assurance of data integrity. In order to address this vital aspect, Cromos Pharma chose to take a fresh look at Risk Based Monitoring procedures and how they might be adapted in each clinical setting to mitigate data risks.

RBM is a not a new concept at all and has long been heralded as an approach that uses proven analytics driven by algorithms to evaluate data at a central level. It further utilizes such insights to direct a remote monitoring process that identifies sites, regions, personnel, study procedures, and patient types requiring additional scrutiny, support, evaluation, or training.

Until very recently, RBM has been wrongly characterized primarily as a means of reducing clinical study costs by reducing travel costs and time spent on site, especially in source document verification of study data. Cost reduction has never been the primary purpose of employing RBM techniques. The primary intent of RBM has always been to ensure data integrity by optimizing a mix of on-site examination and verification of patient data, together with observation of study procedures and site personnel, with a macro-level approach to the analysis of key study metrics and especially those metrics supporting proper randomization as well as critical primary efficacy and key safety endpoints.

A shift to a more data-centric approach to trial management and monitoring

RBM requires a shift in focus from verifying data points on a patient by patient basis, to analyzing comparative data overall to determine whether documented data are consistent with expectations across the study. Sharing of metadata across the industry in recent years has also resulted in the development of powerful analytical tools that can readily identify data inconsistencies (and in some cases, unexpected similarities) that can be used to pinpoint underlying weaknesses in study conduct. These types of analyses provide robust measures to robustly support data integrity remotely, and that certainly applies more than ever during the current pandemic shutdown and most likely, for the foreseeable future.

Growing support for incorporation of RBM processes pre-pandemic

Over the last decade, sponsors, regulatory authorities, and even CROs had begun to question the traditional model entailing routine or interim site visits implemented uniformly across sites with reliance on 75-100% Source Data Verification (SDV).

Growing evidence emerged to question the usefulness of this reliance on SDV, highlighting the potential for errors in this system and suggesting a shift to more data-driven centralized methodologies based on risk assessments factored in at study design level. A 2011 paper examining the potential for central monitoring techniques to replace on-site monitoring found that centralized monitoring activities could have identified 95% of the findings of on-site monitoring visits, less than 1 per cent of which were critical or major in nature.

This led regulatory authorities including theFDA to embrace the RBM concept, which combines centralized and off-site data review with a monitoring process that emphasizes risk identification, management and mitigation, as well as targeted verification of key source documents.

Transcelerate, an industry quality consortium, also argued for “for a shift from excessive concentration on SDV to comprehensive risk-driven monitoring”. In a 2013 position paper it stated by “building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely”.

Despite growing support for the utilisation of RBM in clinical trials over the last couple of decades a lack of consensus remains about how best to advance its role. Many important questions persist including some that are central to the entire concept. For example, what is the correct algorithm to be applied and how can it be used across different types of trials including complex oncology trials and how can it work across all sites, some which may be more experienced than others. In addition, there are concerns about how small sponsors and CROs can effectively use RBM without significant investment.

Cromos Pharma's approach to RBM

- Cromos Pharma embraced the adoption of RBM early on, with the guiding principle that RBM is primarily a tool to improve data integrity.
- Cost savings may result from reduced time on site / CRA travel; but overall, are not always achievable due to procedures other than 100% SDV on site needing to be implemented to ensure data integrity.
- Our experience with RBM has been based upon either sponsor , lead CRO, or Cromos Pharma methodologies and algorithms.
- Our results and results of RBM across the industry have been mixed.
- Part of the reason for ICH E6 R2 guidelines is to emphasize Risk Management in overall study planning and conduct, rather than to rely upon various concepts of RBM alone.
- Accordingly, Cromos Pharma tends to merge RBM with overall risk-based study management procedures to improve data integrity and study conduct overall.

Lasting impacts of forced changes on clinical trials industry

If there is one positive change that the COVID-19 experience has fostered, it is forcing our industry to adopt better, more efficient ways to accelerate innovation and broaden the scope of healthcare provision that will upgrade the quality of medical care for all (e.g. Skype doctors, house calls for research patients, FDA comments provided 'next day,' cross-collaborations between states and countries, “basket studies” evaluating therapies for multiple sponsors in one study). The pandemic-driven shift to increased focus on RBM may also prove to be a tipping point in the conduct of clinical trials. RBM and concomitant platforms that legitimize and improve the effectiveness of virtualization are likely to hasten the journey “from bench to bedside,” and have indelible impact on pharmaceutical research in the post-COVID world.