Worldwide Clinical Trials

The Value of a Hybrid Approach to Medical Monitoring in Early Phase Clinical Development

Marcel Ruiz, MD, Fellow, Clinical Research Methodology, Early Phase Development

In clinical research, particularly within early phase trials, there are several approaches for the role of the medical monitor (MM). While MMs can provide critical services, particularly in indications with high-risk consequences or in Phase I studies with specific patient populations, oftentimes, a hybrid approach is more appropriate. For instance, in healthy volunteer (HV) studies, various contract research organizations (CROs) may offer medical monitoring services through their principal investigator (PI), or the sponsor may utilize their Chief Medical Officer, rather than a dedicated MM.

This position is especially significant in early phase studies, which often involve HVs and require specialized monitoring to manage their unique risks and considerations. This article explores MM's roles and responsibilities, the shift to PI-led MMs, the benefits unique to early phase HV, pharmacokinetics (PK), pharmacodynamics (PD) studies, and additional exploratory objectives, the value of hybrid approaches, and future directions.

MMs are responsible for ensuring trials adhere to strict safety protocols, maintaining trial integrity, verifying regulatory compliance, guaranteeing accurate and reliable data collection, monitoring adverse events (AEs), and more.

The Roles & Responsibilities of a Medical Monitor

Based on the specific study and operational needs, an MM's roles and responsibilities can vary in scope.[1] In Phase I studies, where participants are often HVs, the focus is primarily on safety and tolerability rather than efficacy due to the fact that the primary goal at this stage is to establish the investigational product's (IP) safety profile. MMs are responsible for ensuring the trial is conducted in compliance with the protocol, offering safety oversight, and conducting thorough data review and analysis.

Another primary responsibility of the MM is to review treatment-emergent AEs (TEAEs) in a timely and accurate manner, which is critical to the well-being of study participants. When working with in-house PIs serving as MMs, these professionals are on-site every day, allowing them to monitor AEs or serious AEs (SAEs) in real-time and make immediate adjustments if necessary.[2] This hands-on approach is particularly relevant in single ascending dose (SAD) and multiple ascending dose (MAD) studies, which involve increasing an IP dose to analyze its tolerability, as these patient populations are vulnerable to a greater chance of AEs or SAEs. Both AEs and SAEs are expected to occur in clinical trials, which is why it's the PI's responsibility to provide appropriate medical management when these events arise, rather than to prevent them entirely, as the trial's purpose is to evaluate the biophysiological effects of the IP.

Another key aspect of the MM's role is collaboration, working closely with PIs and site staff to ensure the trial's integrity and compliance. This collaboration ensures that all safety concerns are addressed and

the study adheres to the protocol and regulatory requirements. The MM's multifaceted role necessitates a comprehensive understanding of both the scientific and regulatory dimensions of clinical trials. By fulfilling these responsibilities, MMs are instrumental in the successful execution of clinical research, particularly in the early phases where the groundwork for subsequent studies is established.

Factors Unique to Early Phase vs. Late Phase Studies

While early phase studies concentrate on the initial safety and tolerability of an IP, late phase studies aim to evaluate efficacy and long-term outcomes. Late phase studies often span more than 40 sites, encompassing a greater scale and complexity and typically requiring specialized knowledge of specific disease states, which makes MMs essential to oversee these larger patient populations and evaluate AE trends across the study. MMs must balance the need for rigorous data collection with the practical challenges of managing an extensive, geographically dispersed study population. In contrast, on-site PIs can only provide oversight at their specific unit.

Phase I studies usually involve a smaller number of participants, often at only one to three sites, allowing for continuous monitoring so that MMs can rapidly respond to any AEs as the safety profiles of the IP is unknown at this stage. In Phase I trials, AEs are expected; however, the tolerance for risk in HVs is lower compared to patient populations with significant unmet medical needs due to ethical considerations, as they receive no benefit from treatment. Moreover, when conducting the SAD and MAD first-in-human (FIH) trials, these studies require more attention from MMs at the site level to promote safety and tolerability.

When working with a CRO partner, it can be beneficial to collaborate with one that offers in-house bioanalytical capabilities to ensure timely access to services, such as the ability to run PK/PD tests during SAD and MAD studies to track how HVs are processing new doses. However, not every CRO provides a dedicated site in its network that offers these capabilities.

Important in-house bioanalytical lab capabilities your CRO should have:

- Method transfer
- Assay validation
- Sample analysis with ability to expedite timelines
- PK data analysis
- Off-the-shelf assays

The Shifting Mindset from External Physicians to PI-Led Medical Monitoring

A more integrated approach is replacing the traditional role of employing an external physician or pharmacist as an MM, with the internal PI taking on these responsibilities. This evolution is driven by the need for more continuous and integrated oversight in clinical trials, allowing more seamless site communication with sponsor representatives and potential protocol or dosing adjustments.

When working with a CRO that provides an in-house MM, the PI, being on-site and involved in the day-to-day operations, is able to provide real-time feedback and offer immediate adjustment suggestions to the study protocol, if needed. These changes in the protocol must be approved by the sponsor and the Institutional Review Board prior to these adjustments being made, unless they are for the safety of the subjects.

This heightened level of engagement provides a more thorough and responsive monitoring process, which is crucial in studies where participants' conditions may change quickly. The PI-led MM's presence also helps to foster a stronger sense of accountability and responsibility, leading to overall better trial management, enhanced patient outcomes, and increased rapport with internal teams

In contrast, hiring an external physician can be costly, with up to 10% of the study budget potentially allocated

> When fully in-house, the MM is expected to know the protocol, understand reports, sign off on necessary documents, facilitate necessary reviews, develop a risk management plan, see all the subjects, and provide real-time communications.[3]

for this purpose. Along with the financial implications, many external MMs are often only involved at the beginning and end of the study, which can lead to gaps in oversight and communication. Occasionally, further challenges can arise between internal PIs and external MMs if their exact roles and responsibilities are not clearly outlined at the start of the study, from personality clashes to different testing and clinical significance attributions. It's additionally imperative that the sponsor conduct due diligence when PI-led MM is being considered, such as ensuring that the PI is a full-time, research-dedicated physician with ER and critical care experience, and that the site has appropriate quality control standards and project manager oversight in place.

The Use of a Hybrid Approach

Combining the strengths of PI-led medical monitoring and the use of external MMs, a hybrid approach can offer a balanced and flexible solution, adapting to the individual needs of each study. This model can be particularly beneficial if the external MM is only required to assess the significance of certain tests, which can be more cost-effective and feasible, and is often employed when the sponsor offers a contracted MM versus an internal PI. However, when working with a CRO for your early phase study, ask if they offer an in-house MM, as these professionals often provide considerably more services than an external MM and ensure there is a decreased risk of encountering budget problems.

This hybrid approach can also be effective in addressing gaps in expertise in early phase studies, as while PIs are well-versed in the day-to-day operations of a trial, they may not always have the specialized knowledge required to interpret complex data. For example, an external MM can provide critical insights into biomarker readouts and other specialized analyses, which may be outside of the PI's scope of expertise, ensuring the trial benefits from comprehensive and multidisciplinary oversight.

If a hybrid model is right for your next study, ensure that the external MM's and internal PI's roles are clearly defined in the Standard Operating Procedures (SOPs) and Responsibility Log/Documentation at the start of the study to minimize miscommunications, avoid any overlap, and optimize efficiency. Some additional solutions to combat potential challenges in the hybrid approach are to utilize electronic data management systems to streamline data reviews, ensure all team members are well-trained, and establish clear lines of communication. An eSource data collection system, when used efficiently, can greatly decrease the MM time required and provide timely feedback to site staff and sponsor.

Future Directions for Medical Monitoring

Driven by technological innovations and a growing focus on patient-centric care, substantial advancements in medical monitoring are expected in the future. A notable development is the incorporation of artificial intelligence (AI) into the monitoring process. AI has the capability to analyze extensive data sets in real-time, offering MMs valuable insights that enhance decision-making and patient safety. With AI, MMs can swiftly anticipate potential AEs and trends, ensuring clinical trials are executed with utmost precision and diligence.

Broadening the capabilities of MMs, remote monitoring technologies are emerging to help MMs oversee studies from any global location.[4] For Phase III-IV trials in particular, this new technology may help optimize efficiency and ensure issues are addressed promptly, regardless of the MM's physical location. Real-time data access and communication tools, such as the use of portable and wearable devices, can further enable MMs to stay informed and recommend timely interventions, which is imperative for maintaining the integrity and safety of clinical trials.[5,6]

Conclusion

Medical monitoring is an indispensable service in clinical trials, particularly in early phase studies, from safety oversight and risk mitigation to protocol feasibility and regulatory compliance. As cutting-edge technologies continue to arise in clinical development, these innovations will enhance the MM's ability to offer real-time oversight, enhancing overall trial management and patient outcomes. Moreover, specialization in therapeutic areas and ongoing education will be crucial as the regulatory landscape becomes stricter and personalized medicine approaches gain further prominence. Whether through PI-led MMs, external physicians, or a hybrid approach, the MM's commitment to safety and data accuracy is essential for advancing your study and ensuring the well-being of all study participants.

The authors would like to acknowledge the contribution of Sherilyn Adcock, RPH, PhD and Kirsten Kaiser in the preparation of this manuscript.

References

1. Klein, Gerald and Van Vactor, Susan. Medical Monitor's Essential Role in Clinical Trials. July 1 2025. SSRN: https://ssrn.com/abstract=5336047 or http://dx.doi.org/10.2139/ssrn.5336047
2. Naik, Gurudatte and Saleh, Mansoor. So You Want to Be a Principal Investigator. Journal of Oncology Practice. May 11 2018;14(6) https://doi.org/10.1200/JOP.18.00011
3. Molloy, S.F. and Henley, P. (2016), Monitoring clinical trials: a practical guide. Trop Med Int Health, 21: 1602-1611. https://doi.org/10.1111/tmi.12781
4. Cecconi M, Hutanu AL, Beard J, et al. Unlocking opportunities to transform patient care: an expert insight on limitations and opportunities in patient monitoring. Intensive Care Med Exp. 2025 Feb 22;13(1):24. doi: 10.1186/s40635-025-00733-z. PMID: 39984790; PMCID: PMC11845334.
5. Barone M, Blè A, Costantini C, et al. The importance of medical monitoring in clinical development: The past, present, and future. Applied Clinical Trials. 2021 Dec 22.
6. Li, K., Cardoso, C., Moctezuma-Ramirez, A., Elgalad, A., & Perin, E. (2023). Heart Rate Variability Measurement through a Smart Wearable Device: Another Breakthrough for Personal Health Monitoring? International Journal of Environmental Research and Public Health, 20(24), 7146. https://doi.org/10.3390/ijerph20247146

Worldwide Clinical Trials

About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.