# Risk-based Monitoring Through COVID-19 and Beyond

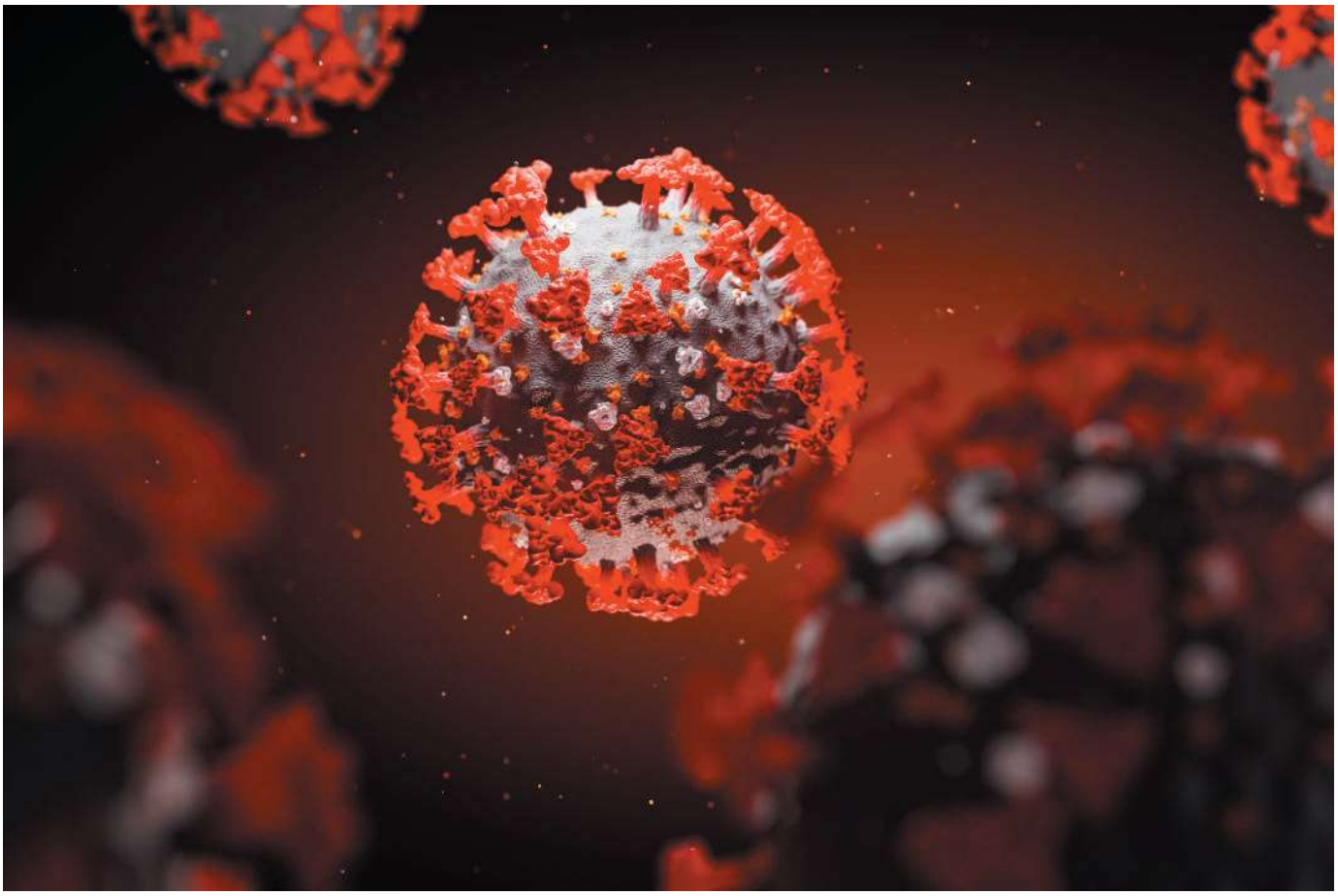
PEER REVIEWED

Risk-based monitoring (RBM) may be a relatively recent phenomenon, but it has become a commonly-used methodology in clinical trials as evidence of its benefits has grown when compared with the limitations of source data verification (SDV). In 2013, both the FDA and the EMA officially embraced the concept of risk-based quality management,[1,2] and paved the way for its practical implementation, and in 2016, the addendum R2 to the ICH-GCP guidelines included explicit expectations around risk-based quality management.[3]

RBM can range from very light to very detailed monitoring strategies, depending on the overall risk level of the trial. However, the focus should always be on the critical data and processes, which support and underpin data quality and subject safety and wellbeing. It is a holistic approach to quality control and therefore involves many different stakeholders, including data managers, central monitors, statisticians and others, all supported by technologies and tools allowing for more and better centralised data review, while facilitating interactions between functional groups via user-friendly interfaces.

By definition, RBM is an adaptive and dynamic approach in which activities in one functional area may trigger actions in another. Risks are reviewed on an ongoing basis and lead to adjustments in the chosen strategy. It is this feature of the methodology that makes it particularly appropriate in these unprecedented times we are witnessing with the COVID-19 pandemic, because it offers guidance on prioritising and how to deal with change in ongoing trials. RBM also uses more remote solutions which can be of great advantage when on-site visits are not possible.

In the current situation, regulators expect trial sponsors to evaluate the potential risks and benefits of their trials, which may result in substantial changes to study protocols, which could lead to changes in the list of critical variables. For example, safety considerations related to COVID-19 could oblige sponsors to adjust withdrawal criteria, or change the inclusion criteria to exclude groups of high-risk patients to minimise the chances of infection by the SARS-CoV-2 virus. Sites that were qualified prior to the pandemic when preventive measures against COVID-19 were not needed may now need to put a process in place to safely allow patients to attend their premises. Other new ways of working could include supplying investigational product direct to patients, switching from central to local laboratories, or from hospital-based measurement to home monitoring and nursing. All of these new approaches have underlying processes that could potentially make a difference to the quality of the trial, and therefore need to be carefully assessed. The list of trial aspects that are now important will no longer be the same as historic ones, and "new" processes and data should be evaluated.



In parallel with the review of critical variables, a new round of risk assessment related to the actual conduct of the trial will have to be initiated. Potential risks include: trial participants and staff being infected with COVID-19; a higher subject drop-out rate due to travel limitations and self-isolation; more protocol deviations resulting from communication difficulties, last-minute changes to protocols, and altered visit schedules; and recruitment being halted or delayed to the extent that the initial sample size will not be achieved and the statistical power could be reduced.

Once a new set of risks has been identified and assessed, the decision must be made as to whether the risk would substantially change the outcome of the trial or affect subject safety, and whether it can be prevented or mitigated, transferred to another party or accepted within certain tolerance limits. One way of managing risk is by adapting trial oversight activities at the programme, study, country, and site level. For new risks, a suitable indicator needs to be determined, while already existing indicators may also need to be adjusted.

The next step is to adjust the monitoring strategy in accordance with the outcome of the risk assessment and to find a good balance between what can be done on-site and what activities can be done remotely. The result should be a new monitoring plan with different emphases, but in which the sum of the different monitoring approaches still offers an effective strategy for ensuring quality oversight with focus on critical aspects.

Obviously, the first priority is to protect the safety, rights and wellbeing of trial participants, which means keeping the focus on critical areas. At the same time, the extent and nature of oversight measures must be weighed against the extra burden for the site under these exceptional circumstances. Depending on restrictions, urgency, and availability of staff, it could make sense to cancel or postpone on-site monitoring activities – at least for a certain period – or to amend the schedule of subsequent visits to reduce risks.

If on-site activities are being reduced, remote monitoring activities can be intensified both in frequency and extent, such as more regular remote electronic case review form (e-CRF) review, and extending the number of electronic data capture reports to be checked by monitors and medical monitors. In some instances, remote SDV may be possible depending on the processes or systems in place at individual sites, so the monitoring plan should be flexible. Centralised monitoring capabilities can also be expanded, including new key risk indicators (KRIs) and more frequent data surveillance. The outcome and trends can be used to prioritise remote and on-site activities.

There are drawbacks to using the centralised method, and these include the need for statistical analysis software, a separate independent central monitoring team and the requirement for large subject numbers, which may rule out some smaller projects from adopting the method. Regional stay-at-home orders may reduce the reliability of site quality assessments, while the lack of on-site staff or staff turnover may cause a delay in data entry, thereby delaying central analysis of KRIs.

In these cases, remote visits are essential to maintain subject safety and data integrity, and to ensure study endpoints are protected. Some items may still need to be undertaken or revisited during an on-site visit.

In these exceptional circumstances, ensuring the team is prepared for an on-site visit becomes a high priority, and a decision tree can be implemented on a case-by-case basis to ensure such a visit is indeed possible. The team should be instructed on how to conduct on-site

visits safely, with regard to personal hygiene and social distancing, and the provision of the correct personal protection equipment. Safety, as ever, is paramount.

Some of the changes being implemented during the current pandemic may become permanent, but others should be considered temporary measures. Follow-up measures need to be planned ready for implementation when the situation is normalised, including increased on-site monitoring; rectifying any problems at the site that could not be resolved during lockdown; re-monitoring of critical data; and proper documentation of deviations.

The current situation can be used as an opportunity to learn and take remote processes to the next level. Certainly it requires more weight to be put on centralised approaches, but not to the exclusion of on-site activities – both are still needed.

**REFERENCES**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## Steven Thys

Steven Thys has more than 19 years' experience within the pharmaceutical and drug development industry, and before joining SGS in 2019, held a number of positions in clinical operations at Servier. These included Director of Global Trial Management where he was responsible for delivering the company's portfolio of Phase I-IIIb trials in a variety of therapeutic areas. Mr Thys graduated as a pharmacist from the University of Leuven, and holds a master's degree in medical & pharmaceutical research from the University of Brussels (VUB).