Are Preventive Approaches to Clinical Trial Quality Management Cost-Effective?

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Dr. María Proupín-Pérez, PMP
Project Leader at PPH plus
Co-authored by Dr. med. Johanna Schenk, Managing Director & COO,
PPH plus GmbH & Co. KG

Biopharma is challenged to bring new medicines to the market by overcoming the growing regulatory, cost and time constraints. Despite of intense and costly quality control and assurance (QC & QA) measures, comprising standard operating procedures (SOPs) and dedicated quality management (QM) functions, regulatory compliance issues are not uncommon.[1]

One of the key QM processes is clinical monitoring, which has been traditionally supported by 100 % source data verification (SDV) at clinical sites (on-site). As an example, only the clinical monitoring for a large global clinical trial (14,000 patients, 300 sites) costs about 90 million USD (30 %) out of a total budget of 300 million USD[2]. The QM system is composed of further processes apart from monitoring. Therefore, QM would have a higher cost. Even though QC & QA is so costly, quality is not yet accomplished and asks for new efforts to revise and renew the clinical trial (QM) system. These efforts may originate additional QM costs, which biopharma would prefer avoiding or may hardly afford, depending on the organizational size or accessible resources. Moreover, these QM extra efforts are actually preventive actions that some organizations may distrust or perceive as of uncertain value. A direct comparison of QM costs derived from the implementation of non-preventive and preventive procedures is difficult. The aftermaths can be inaccurate and fallacious.

How can you check whether preventive actions are actually excessive, inefficient or unnecessary? Check past projects and review how much time and personnel has been required, as example, to perform the following activities during the clinical trial closure phase:

- Review the final trial master file (TMF) to ensure inspection readiness after neglectful TMF maintenance
- Reconcile investigational medicinal product (IMP) accountability at patient, site, depot and study level
- Review, follow-up on and solve issues at different clinical trial locations
- Implement corrective action preventive actions (CAPAs) to comply with auditors' requests concerning major and critical findings

The sum will be a good indicator of how much you could invest in preventive actions before and during clinical study conduct. QM costs are "reproducible" and, therefore, predictable. Issues observed in more than one trial will most probably arise again in the future. Appropriate QM does not seek perfection but the prevention of these recurrent or systematic failures instead. Surprisingly, there is still reluctance to invest in preventive approaches, possibly because repairing mistakes has not clearly been identified as rework yet. *Change quality management* may require just better planning in organizations with non-critical issues. Others may, however, need to undergo massive restructuring and dismiss old procedures to create a completely new QM system.[3]

New technologies are solving some QM burdens, such as the remote monitoring of clinical data by means of electronic data capture (EDC) systems. Thus, many QM activities can now be implemented timely or at least faster than with paper-based data collection procedures. Nevertheless, the way these technologies have been implemented is not always beneficial from the QM perspective. In some cases quality is neglected as clinical data and procedures have been barely evaluated from central locations. There are mistakes that a computer will detect better than the human eye, but there are inappropriate procedures that only human beings notice. On the other hand, not all technologies are fit for purpose and, instead of enhancing quality, may jeopardize patient safety surveillance and clinical data reliability. Thus, novel IT systems provide great support to clinical trial oversight but still need an investment to be adjusted to quality requirements.

The above-mentioned elements are not the only aspects to be analyzed concerning QM costs. The following compliance issues are of higher importance and should be taken in consideration:

- Missing signatures for first clinical supply release or other relevant authorizations
- Safety issues derived from inappropriate IMP storing conditions or IMP administration to ineligible patients, as well as
- Missing source data, such as medical records for source data verification

All of these are mistakes that cannot be corrected retrospectively and put at risk patients' health. Thus, **there are additional ethical reasons to change neglectful mindsets**. Exposing patients to novel treatments to capture unreliable data concerning drug safety and efficacy is as well ethically questionable. Patient centricity must be understood as avoidance of pointless exposure to treatments, too. Trials terminated due to QM issues are an example of this unnecessary exposure. That is one of the main reasons why drug developers should deploy responsible planning for timely evaluation of risk-proportionate QM activities before starting a clinical trial. Patient safety and clinical data integrity should not rely on sole clinical monitoring practices, but on a holistic QM system.

Consequently, QM costs go beyond the clinical trial budget given that quality pitfalls very often cannot be redeemed by sudden late rescue measures.

The risk-based QM paradigm shift primarily seeks the prevention of the above-mentioned irreparable hazards, such as potential health damage caused to patients. Costly and laborious rework occupies the second place, despite of its business relevance. Thus, the above patient centricity demanded by a proper QM system brings huge savings in time and data reliability. That is a good reason to rely on safer preventive QM approaches avoiding rework from the start. QM cost-effectiveness is not just related to the overall clinical study expense.

Dr. María Proupín-Pérez, PMP
Project Leader
PPH plus GmbH & Co. KG

Dr. med. Johanna Schenk
Managing Director & COO
PPH plus GmbH & Co. KG

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