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Review Article

The quality debt of clinical trials: how small operational deviations accumulate into scientific and regulatory risk

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ABSTRACT

Clinical trial quality depends on several interconnected processes that protect participants and support the reliability of study data. Protocol deviations, audit findings and corrective and preventive action (CAPA) records help identify quality concerns. However, the number of recorded findings and their administrative closure status may not fully reflect the residual risk within a clinical trial. This review introduces the concept of quality debt in clinical trials to examine quality vulnerabilities that develop or persist during trial conduct. A conceptual review was undertaken using selected regulatory guidance and scientific publications addressing good clinical practice, quality by design, risk-based monitoring, protocol deviations, protocol complexity and clinical trial quality management. The literature was examined to develop a working definition and identify potential dimensions of the proposed concept. The objective was conceptual development rather than systematic evidence synthesis. Quality debt is proposed as a framework for examining residual quality risk arising from deficiencies that persist, recur, interact or remain inadequately controlled despite corrective actions. Five candidate dimensions were identified: criticality, persistence, recurrence, remediation effectiveness, interaction and residual risk. Together, these dimensions encourage consideration of the underlying quality conditions rather than relying solely on event counts or administrative closure status. Quality debt may offer an additional perspective on how unresolved quality vulnerabilities accumulate during clinical trial conduct. However, the concept remains theoretical, and its dimensions have not been operationally defined or validated. Further research is needed to determine whether it provides meaningful information beyond existing clinical trial quality-management approaches.

Keywords: Clinical trials quality, Risk-based quality management, Protocol deviations, Corrective and preventive action, Quality by design, Residual risk

INTRODUCTION

Clinical trials depend on several interconnected processes to protect the participants and generate reliable scientific evidence. Informed consent, eligibility assessment, safety surveillance, investigational product management, data collection and study oversight all contribute to trial quality.[1,2,8] Weakness in one area can affect other aspects of study conduct, particularly when an operational deficiency remains undetected or inadequately addressed.

Current regulatory guidance, including ICH E8(R1) and ICH E6(R3) emphasises quality by design and risk-based approaches to clinical trial management. These approaches encourage the identification of factors critical to participant protection and data reliability, with appropriate controls established throughout the study lifecycle.[1-4,8,11] Quality-management systems capture events such as protocol deviations, audit observations, monitoring findings, and CAPA records. Although essential for documenting issues and corrective action, administrative

closure does not necessarily demonstrate that the underlying weakness has been resolved.[5,9,19-21]

For example, repeated deviations involving incomplete safety assessments may be recorded and closed individually. However, if their underlying cause is inadequate investigator oversight, insufficient staff training or weaknesses in site-level review, similar deficiencies may continue. Assessing each event in isolation may therefore provide an incomplete picture of the quality risk affecting the study.

The significance of a finding cannot be determined by its classification or closure status alone. Its potential impact, duration, recurrence, relationship with other deficiencies and the effectiveness of corrective measures also warrant consideration. A critical deficiency may require immediate intervention, while a lower-risk finding may remain adequately controlled through documented interim measures.

Against this background, this article introduces quality debt in clinical trials, defined as the residual quality risk associated with deficiencies that persist, recur, interact or remain insufficiently controlled, even after individual corrective actions have been formally completed. Drawing an analogy with technical debt, the concept highlights how unresolved weaknesses may create further complications as a system evolves. In clinical research, the concern is not simply the accumulation of open records, but the potential for inadequately controlled deficiencies to affect interconnected processes and compromise trial quality.

Quality debt is proposed as a complementary perspective within existing quality-management systems, not as a replacement for risk-based quality management, CAPA procedures, quality tolerance limits or established oversight mechanisms. It is also not intended to measure staff, investigator, site or organisational performance. Rather, it encourages consideration of the residual risk following identification and corrective action.

This review aims to establish a working definition of quality debt, examine its relationship with existing quality-management approaches, describe its potential dimensions and identify the research needed to assess its practical relevance. The framework remains conceptual and has not yet been validated as a measurement tool, established as a regulatory construct or shown to predict clinical trial outcomes.

SCOPE AND WORKING DEFINITION

For this review, quality debt in clinical trials is defined as the residual quality risk associated with deficiencies that persist, recur, interact or remain inadequately controlled despite corrective or preventive measures. The term refers to the condition of the quality system and the effectiveness of its controls, rather than the performance of individual staff members, investigators, sites or organisations.

The concept requires consideration of several related factors. First, the importance of the affected process must be understood in relation to participant protection, data integrity and the reliability of study conclusions. Second, the history of the deficiency should be considered, including whether it has persisted or recurred. Third, the adequacy of the corrective action and the evidence supporting its effectiveness need to be examined. Finally, consideration should be given to whether deficiency relates to weaknesses in other processes and what level of risk remains.

Protocol deviation, by itself, should not be interpreted as evidence of quality debt. The significance of a finding depends on its circumstances and the effectiveness of the controls in place. Similarly, the length of time an issue remains open is not sufficient to establish its importance. A lower-risk finding may remain open while effective interim controls are maintained and documented. In contrast, a newly identified deficiency affecting a critical-to-quality factor may require immediate escalation.

The administrative closure of a CAPA also requires careful interpretation. Completion of the documented action does not, on its own, demonstrate that the root cause has been addressed or that the implemented control is effective. Equally, an open action does not automatically indicate that risk is unmanaged, provided appropriate interim safeguards are operating and their effectiveness can be demonstrated. These distinctions are central to the proposed concept and are summarised in Table 1.

LITERATURE SEARCH APPROACH

A targeted literature review was undertaken to identify published research and regulatory guidance relevant to the proposed concept of quality debt in clinical trials.[1-4] The review focused on established approaches to clinical trial quality management, including quality by design (QbD), risk-based monitoring (RBM), quality tolerance limits (QTLs), protocol deviation management, CAPA effectiveness, clinical quality-management systems and protocol complexity. Relevant principles described in ICH E6(R3) and ICH E8(R1) were also considered.[1,2]

The search strategy used relevant free-text keywords and controlled terms, such as medical subject headings (MeSH) where available. The main search concepts included “clinical trials as topic,” “quality assurance, health care,” “quality control,” “risk management,” “risk assessment,” “patient safety,” “quality improvement,” “data integrity” and “clinical protocols”. The search concept also used free-text terms such as “clinical trial quality,” “clinical quality management,” “risk-based quality management,” “quality by design,” “risk-based monitoring,” “protocol deviations,” “corrective and preventive action,” “CAPA effectiveness,” “protocol complexity,” “residual quality risk” and “data reliability”. The search strategy combined these terms using Boolean operators, as appropriate to the database and, for what was

being explored. Additional publications were identified by examining the reference lists of relevant articles and guidance documents.

Relevant material was identified from bibliographic databases, regulatory guidance documents, peer-reviewed publications and institutional or industry resources. Reference lists of relevant publications and guidance documents were also examined to identify additional material.

The review was intended to support the development of a conceptual framework rather than provide a comprehensive assessment of all available evidence. No formal systematic review protocol was established. Database-specific search strategies, independent duplicate screening and PRISMA-based study selection were not undertaken.

The selection of literature was therefore targeted and interpretative. The proposed framework and any assessment of its potential contribution should be considered preliminary. A reproducible and comprehensive evidence synthesis will be necessary to examine the concept more systematically.[2-4]

MAIN SOURCE GROUPS IDENTIFIED

The literature considered in this review included established approaches to clinical trial quality management. These included ICH E6(R3), ICH E8(R1), the clinical trials transformation initiative (CTTI) quality by design initiative and transcelerate's clinical quality management system (CQMS) framework. Relevant publications on protocol deviation management, risk-based monitoring, protocol complexity, and clinical trial site-performance assessment were also considered.[1,2,5-11]

These approaches address important aspects of trial quality. They provide principles and practical mechanisms for identifying critical processes, anticipating risks, monitoring study conduct, investigating deviations and implementing corrective actions.

However, the literature considered here suggests an area that warrants further examination: how the residual risk associated with a deficiency change when the problem persists, recurs, or affects other processes despite individual corrective actions.[9,19,24]

The proposed quality debt concept focuses on this question. It does not assume that existing quality-management systems fail to identify such problems. Rather, it considers whether a more explicit longitudinal assessment of unresolved quality vulnerabilities could help explain the relationship between individual quality events and the overall risk condition of a clinical trial. Whether this perspective offers information beyond existing systems remains to be established.

RELATIONSHIP TO ESTABLISHED QUALITY-MANAGEMENT APPROACHES

Quality by design and critical to quality factors

QbD provides a structured approach to identifying factors that are critical to participant protection and the reliability of clinical trial results.[1,2,8,11] It encourages sponsors to consider potential risks during study planning and to incorporate appropriate controls into the protocol, processes, and oversight arrangements.

The proposed quality debt concept addresses a different stage of the quality-management process. Even when risks have been identified during planning and suitable controls have been established, weaknesses may arise during implementation. Controls may not be followed consistently, may prove insufficient under actual study conditions or may lose effectiveness as trial activities progress. A longitudinal assessment of these weaknesses could help identify whether the risk originally addressed through QbD remains adequately controlled.

For example, a protocol may include clear requirements for timely safety assessments, supported by investigator training and monitoring procedures. If these controls are not consistently implemented on a site, the resulting deficiencies may extend beyond individual deviations. The proposed framework would consider whether the underlying risk remains controlled and whether related weaknesses require attention. The extent to which this approach adds value to established QbD practices requires further investigation.

Risk-based monitoring and clinical quality management

Risk-based monitoring and clinical quality-management systems provide established mechanisms for identifying important risks, prioritising oversight activities, analysing trends and implementing appropriate mitigation measures.[2-4] These systems also support the investigation of recurring findings and the assessment of corrective actions. The question considered in this review is whether the residual risk associated with a deficiency remains adequately controlled after the relevant action has been completed.

The proposed quality debt concept builds on these established activities by placing particular emphasis on the status of residual risk over time. A finding may be closed in the quality-management system, yet the underlying control may remain ineffective. Similarly, several apparently unrelated findings may have a common cause that is not readily apparent when each is reviewed separately.[10,12,13,25]

The practical question is whether the assessment of these relationships can improve existing quality-governance decisions. For instance, repeated data-entry errors, delayed query resolution and incomplete source documentation

may arise from a common weakness in site processes or oversight. Reviewing these issues together may provide a more complete understanding of the risk than considering each record independently.

However, risk-based quality management already allows such issues to be identified and evaluated. Research is therefore needed to determine whether quality debt offers a distinct analytical contribution or simply provides another way of describing activities that are already performed through QTLs, key risk indicators (KRIs), CAPA systems and routine quality oversight.

Protocol deviation lifecycle management

The management of protocol deviations involves their identification, classification, documentation, investigation and appropriate corrective action. Previous work has described the importance of managing deviations throughout the clinical trial lifecycle.[5] The proposed framework raises a related question: after a deviation has been investigated and the corrective action implemented, what evidence demonstrates that the underlying vulnerability has been controlled? It also considers whether similar deficiencies have appeared in other processes or at later stages of the study.[5,20,21]

This distinction is relevant because the closure of an individual deviation does not necessarily establish that the broader problem has been resolved. For example, repeated deviations involving eligibility assessments may reflect an underlying weakness in staff training, source-document review or investigator oversight. A review limited to individual deviation records may not adequately identify the wider issue.

Nevertheless, linking findings requires a sound basis. Similar descriptions do not necessarily indicate a common root cause, and inappropriate grouping may lead to misleading conclusions. Any assessment of quality debt would therefore require reliable classification, documented investigation findings and defensible criteria for identifying related deficiencies.

Protocol complexity and site-performance measures

Recent publications have addressed the development of tools for assessing protocol complexity and clinical trial site-performance. A protocol-complexity tool has been proposed to facilitate discussion of study design and execution burden, while research has also examined the development of a clinical trial site-performance metrics instrument.[6,7]

These approaches address different aspects of clinical research. Protocol complexity concerns the demands placed on study conduct by the design and requirements of a trial. Site-performance measures examine performance against specified indicators. The proposed quality debt framework, in contrast, focuses on the residual risk associated with deficiencies that persist, recur or interact during trial conduct.[16,17]

For example, a complex protocol may place substantial demands on investigators and site staff, but complexity alone does not establish that quality has been compromised. Similarly, a site may perform well against routine performance indicators while retaining an unresolved weakness in a process critical to participant protection or data reliability.

The distinction is therefore not one of superiority. Each approach addresses a different question. The contribution of quality debt, if any, would depend on whether it provides a more useful understanding of unresolved quality vulnerabilities than the information already available through complexity assessments and site-performance measures.[7,23]

What the comparison establishes- and what it does not

Literature provides a basis for examining the proposed concept, but it does not establish that the concept represents a distinct or validated construct. Existing quality-management approaches already address risk identification, deviation management, corrective action and trial oversight. The potential contribution of quality debt lies in examining whether residual risk continues after a deficiency has been identified and addressed, particularly when the problem persists, recurs or affects connected processes.

Whether this focus warrants a separate conceptual framework is an open question. Further research should establish whether it offers a meaningful contribution to clinical trial quality management or whether the same considerations can be incorporated more effectively into existing quality-management practices.

PROPOSED CONCEPTUAL FRAMEWORK

Five candidate dimensions

The proposed quality debt framework comprises five candidate dimensions, presented in Table 2 and illustrated in Figures 1 and 2. These dimensions represent areas that may help assess the nature and extent of residual quality risk. They are intended as conceptual domains rather than components of a validated measurement scale. No numerical score or weighting system is proposed at this stage.

The dimensions are interrelated and should not necessarily be interpreted in isolation. A deficiency affecting a critical process may require immediate attention even if it has only recently been identified. Repeated findings may indicate an ineffective corrective action, although recurrence should be established through a meaningful comparison of the underlying events. Similarly, the presence of several findings does not automatically indicate that they are

connected. Their relationship must be supported by investigation findings or other relevant evidence.

The fifth dimension brings together two related considerations: the interaction between deficiencies and the residual risk that remains after mitigation. This distinction is important because the presence of connected weaknesses may increase the overall vulnerability of a study, even when individual findings appear to have limited consequences.[1-4,8,9,11,19-22,24]

Proposed pathways

Under the proposed framework, quality signals are considered in relation to their potential impact on participant protection, data integrity and the reliability of trial results. Once a deficiency is identified, its significance depends not only on the initial finding but also on the investigation, the corrective measures implemented and the evidence available to demonstrate that the underlying problem has been addressed.

Corrective action may resolve the immediate issue without eliminating the cause. For example, retraining site personnel may address an identified knowledge gap, but it may not be sufficient if the problem also involves inadequate supervision, unclear delegation or weaknesses in the site's review procedures. In such circumstances, the original deficiency may recur or appear in another process.

The assessment of quality debt would therefore need to consider the relationship between the original findings, the investigation, the corrective measures implemented and the risk that remains. Residual risk may persist when the underlying cause has not been adequately addressed, when an intervention fails to produce sustained improvement or when related weaknesses remain unidentified. By contrast, effective corrective measures and well-documented interim controls may substantially reduce risk even when an administrative action remains open.

The progression of quality risk should not be assumed to be linear. A deficiency may improve following intervention, remain unchanged, recur or become more significant when new information emerges. A critical issue may require immediate escalation regardless of how long it has remained open or whether similar findings have been recorded. For this reason, quality debt should not be assessed solely through the number of open findings, their duration or the frequency of recurrence. The effectiveness of existing controls and the consequences of the remaining risk must also be considered.

Equal counts, different context

Consider two clinical trials with the same number of documented protocol deviations. In the first trial, the deviations are minor, promptly investigated and effectively addressed. Subsequent review provides no evidence of recurrence, and appropriate controls remain in place.

In the second trial, several deviations affect a process important to participant protection or data reliability. Similar problems continue to occur despite corrective actions, and there is limited evidence that the underlying causes have been adequately addressed.

Although the number of recorded deviations is identical, the quality conditions in the two trials are clearly different. In the first, the available evidence suggests that the issues have been controlled. In the second, the recurrence of deficiencies and uncertainty about the effectiveness of remediation indicate that further assessment may be necessary.

This comparison illustrates why event counts alone may not provide an adequate understanding of clinical trial quality. The proposed quality debt concept encourages consideration of the circumstances surrounding each finding and the extent to which risk remains after corrective action. It does not, however, establish that a trial with greater residual quality risk will necessarily experience poorer scientific, operational or regulatory outcomes.[3-5,9,24] Such relationships would need to be examined empirically (Figure 3).

Propositions for empirical examination

The proposed framework raises several questions that require empirical examination. The number of documented quality events and their administrative status may not fully reflect the residual quality risk within a clinical trial, particularly when the criticality, persistence, recurrence and effectiveness of remediation are not considered. Deficiencies that persist or recur despite corrective action may be associated with greater residual risk than isolated findings that are promptly and effectively addressed. The extent of any such relationship, however, is likely to depend on the nature of the deficiency, the circumstances of the trial and the effectiveness of the controls in place.

A further question concerns the relationship between findings identified across different clinical trial functions. Examining related findings collectively may help identify common causes or interconnected weaknesses that are not apparent when individual events are reviewed separately. It remains to be established whether a longitudinal assessment of residual quality risk provides additional information beyond conventional deviation management, CAPA systems, risk-based quality management and site-performance measures.

Any association between the proposed quality debt concept and operational, scientific or regulatory outcomes may also be influenced by factors such as detection practices, reporting culture, trial complexity, study phase and the effectiveness of existing quality systems. These

considerations should be examined through appropriately designed studies. Research will need to establish whether the proposed dimensions can be defined consistently, whether different reviewers reach comparable assessments and whether the resulting information improves quality-related decisions.

PRACTICAL IMPLICATIONS

If the construct proves useful

If further research establishes that quality debt provides a meaningful additional perspective, its practical value may lie in supporting more informed quality-governance discussions rather than introducing another performance measure.[3,4] When a significant quality issue is reviewed, decision-makers need to understand the nature of the deficiency, its potential consequences, the underlying cause, the corrective measures implemented and the evidence supporting their effectiveness. The status of interim controls and the level of risk that remain after intervention also need to be considered.[26]

The proposed approach may also encourage a broader examination of related findings. For example, repeated delays in safety reporting, incomplete documentation and inadequate follow-up may initially be recorded as separate operational issues. Where investigation establishes a common cause, such as insufficient investigator oversight or inadequate site-level processes, addressing the findings collectively may be more appropriate than treating each one as an isolated event.

Table 3 presents governance questions that could support such an assessment. These considerations are intended to complement existing quality-management procedures and should not be interpreted as a replacement for established decision-making requirements.

Any application of these considerations should remain within the sponsor's established quality-management system and applicable regulatory requirements. The assessment must not delay urgent action or interfere with existing safety-reporting, escalation, QTL management, audit, or inspection processes.

Table 1: Comparison of the proposed quality debt concept with related quality management constructs.

Related concept	Primary question it answers	How the proposed construct differs
Deviation/finding count	How many events or observations were recorded?	Considers persistence, recurrence, interaction and residual risk, not count alone
CAPA status	Was the corrective action opened, completed and closed?	Ask whether the underlying risk is demonstrably controlled, not only whether workflow status changed
Risk-based monitoring/RBQM	How should trial risks be identified, prioritised, monitored and mitigated?	Would examine the longitudinal residue of risks that persist despite the existing system; it does not replace RBQM
Quality by design/critical-to-quality factors	How can important risks be anticipated and controls designed into the trial?	Focuses on whether execution weaknesses and ineffective controls accumulate during conduct
Protocol complexity measures	What features make a protocol difficult to execute?	Focus on realizing, unresolved quality vulnerabilities over time rather than design complexity itself
Site-performance measures	How is site-performance described across defined indicators?	Is not intended as a site ranking; it focuses on evolving residual quality risk across processes and time

Table 2: Five candidate dimensions.

Dimension	Working interpretation	Questions for assessment
Criticality	Importance of the affected process to participant protection, data integrity, or reliable interpretation of study results	What could be affected? is the process critical to quality? what are the plausible consequences?
Persistence	Duration for which an issue remains unresolved or inadequately controlled	How long has vulnerability existed? what interim controls are in place, and are their effectiveness documented?
Recurrence	Reappearance of the same or a related deficiency following intervention	Has the issue occurred previously? is the apparent recurrence comparable to the earlier finding?
Remediation effectiveness	Extent to which corrective actions address the underlying cause and produce demonstrable improvement	Was the root cause adequately investigated? what evidence demonstrates that corrective action is effective?
Interaction and residual risk	Relationship between connected deficiencies and the level of risk remaining after mitigation	Are findings associated with a common cause or control weakness? what risk remains after the measures taken?

Table 3: Governance questions and decision considerations for assessing quality debt in clinical trials.

Governance question	Evidence to examine	Potential decision
Is the issue critical?	Affected critical-to-quality factor, participant-protection implications and data impact	Prioritise response according to consequence and applicable requirements
Is the risk currently controlled?	Interim controls, implementation evidence, monitoring of control performance	Maintain, strengthen or replace interim control
Has the issue persisted or recurred?	Timeline, comparable prior findings, prior actions and recurrence evidence	Reopen investigation or broaden root-cause assessment where justified
Are findings connected?	Shared workflow, system, training, vendor, oversight or governance cause	Consider cross-functional corrective action rather than isolated closure
Was remediation effective?	Prespecified effectiveness criteria, follow-up evidence and recurrence surveillance	Close with documented rationale, extend follow-up or revise action
What residual risk remains?	Current exposure, uncertainty, control status and potential consequences	Escalate, accept with documented rationale, mitigate further or monitor

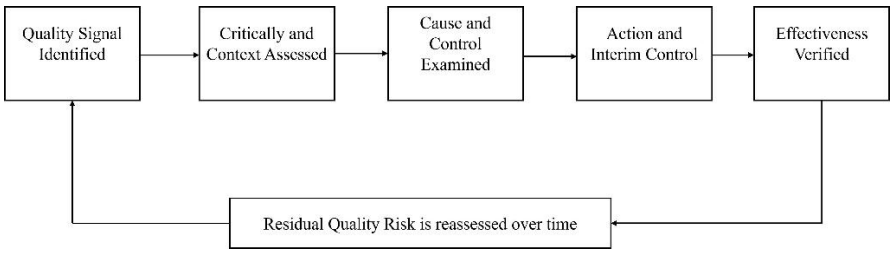


Figure 1: Lifecycle of unresolved quality risk, the diagram illustrates possible pathways through which deficiencies may persist, recur, or interact despite corrective actions, the pathways are conceptual and do not represent established causal relationships.

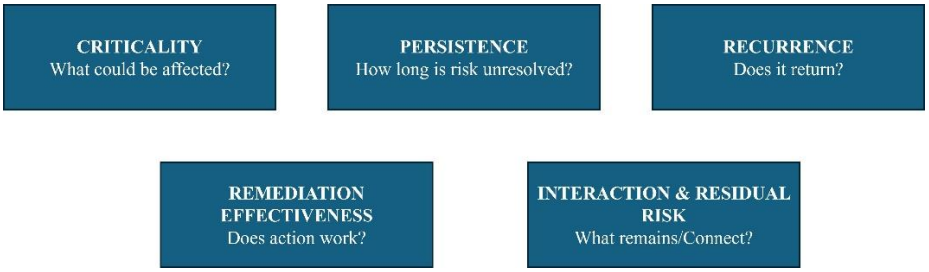


Figure 2: Five candidate dimensions of quality debt in clinical trials, the dimensions represent proposed areas for assessing residual quality risk and require further operational definition and validation.

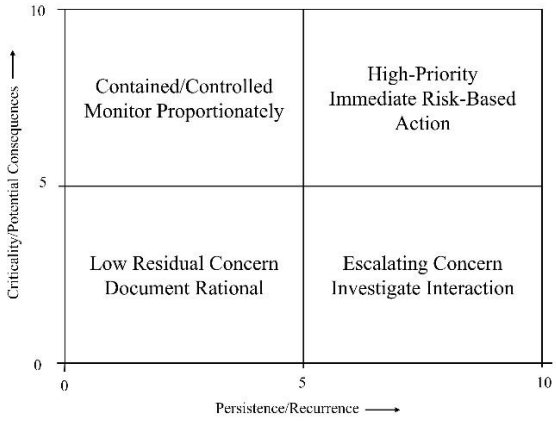


Figure 3: Conceptual prioritisation framework for examining residual quality risk, the illustration is intended to support quality-governance discussions and is not a validated scoring system or a substitute for trial-specific risk assessment.

SAFEGUARDS AGAINST MISUSE

Any approach that examines accumulated or residual quality risk needs to be applied with care. If quality debt were used to rank or compare sites, investigators, or organisations, it could create unintended consequences. Staff might become reluctant to report quality concerns or initiate investigations if a higher number of recorded findings were interpreted as evidence of poor performance. Such an approach could undermine the transparency that an effective quality-management system is intended to support.

The frequency of reported findings also depends on the effectiveness of surveillance and reporting systems. An organisation with a well-established monitoring programme may identify and document more deficiencies than one with less effective oversight. A higher number of recorded findings should therefore not automatically be interpreted as poorer underlying quality.

Any future application of the quality debt concept should distinguish between the identification of quality events and the level of residual risk associated with them. Assessments should consider the effectiveness of interim controls, the adequacy of corrective actions and the evidence supporting the closure of identified deficiencies. A non-punitive quality culture is also important to ensure that staff and investigators continue to report problems without fear of inappropriate performance-related consequences.

Comparisons across sites or studies should be avoided until consistent definitions and reliable assessment methods have been established. Differences in trial complexity, monitoring intensity, reporting practices, and organisational quality systems may influence the number and nature of findings identified.

Most importantly, an aggregate assessment must never delay action on a critical quality issue. Deficiencies that could affect participant safety or the reliability of important trial data require timely investigation and appropriate escalation, irrespective of any overall quality debt assessment. Until the concept has been adequately evaluated, it should not be used as a compliance measure, contractual benchmark, or indicator of individual performance.[19-22]

RESEARCH AND VALIDATION AGENDA

The immediate priority is to determine whether quality debt can be consistently defined and assessed and whether it provides information beyond existing clinical trial quality-management approaches. Developing a numerical score at this stage would be premature. Conceptual refinement and empirical evaluation should come first.

A comprehensive literature review, supported by documented search strategies and transparent selection criteria, would help clarify the relationship between quality debt and established quality-management approaches. The working definition and proposed dimensions should also undergo multidisciplinary review involving investigators, sponsor and CRO quality professionals, clinical operations personnel, data managers, pharmacovigilance specialists, statisticians and regulatory experts.

Clear operational definitions are then needed for issue onset, criticality, persistence, recurrence, control implementation, remediation effectiveness, interaction and residual risk. Particular attention should be given to distinguishing genuine recurrence from similar findings arising from unrelated causes. Retrospective feasibility studies using appropriately governed, de-identified quality-management data could establish whether the required information is available and whether related findings can be consistently linked.

Assessment reliability should subsequently be examined through independent reviews of selected quality findings, with particular attention to agreement on criticality, recurrence, remediation effectiveness and residual risk. The framework should also be compared with existing indicators, including deviation counts, CAPA metrics, QTLs, KRIs, RBQM outputs and site-performance measures, to determine whether it identifies vulnerabilities or supports decisions beyond existing approaches. Potential unintended consequences, such as under-reporting, punitive application, excessive risk aversion and inappropriate study comparisons, must also be considered.

Further evaluation across sponsors, CROs, therapeutic areas, trial phases and study designs would help establish the framework's broader applicability. Such studies should account for detection bias and confounding factors, including monitoring intensity, protocol complexity, reporting practices, duration of exposure and data quality. More intensive monitoring, for example, may increase the number of recorded findings without necessarily indicating weaker quality controls.[12,13,26]

Any association between quality debt and operational, scientific or regulatory outcomes must therefore be interpreted cautiously. Evidence of consistent assessment and incremental value is essential before considering the framework for routine application.

Limitations

This article is a conceptual review based on a targeted selection of relevant literature rather than a systematic assessment of available evidence. Although the literature was selected to support the development of the quality debt framework, selection bias and incomplete coverage of relevant publications cannot be excluded.

The proposed framework and its five candidate dimensions have not undergone formal consensus

development, reliability testing or empirical validation. Their definitions and relationships require further examination. In particular, assessing interactions between findings and estimating residual risk may involve reviewer judgement unless clear operational criteria are established.

The analogy with technical debt provides a basis for discussing accumulating weaknesses but may not fully capture the dynamic nature of clinical trial quality management. Quality risks can change following interventions, emerging information or changes in study conduct. Interim measures may also adequately control a risk even when the associated administrative action remains open.[27,28]

Furthermore, the framework overlaps with established approaches, including risk-based quality management, CAPA procedures, quality tolerance limits and broader clinical quality systems. Whether quality debt represents a distinct construct or an additional interpretation of information already captured by these systems remains uncertain.

Finally, no empirical relationship has been established between quality debt and participant safety, data integrity, scientific validity or regulatory outcomes. Such relationships require appropriately designed studies and should not be assumed. Until then, the framework should be regarded as a concept for further investigation, not an established method of assessing clinical trial quality.

CONCLUSION

Quality debt in clinical trials is proposed as a framework for examining residual quality risk associated with deficiencies that persist, recur, interact or remain inadequately controlled despite corrective actions. The concept draws attention to an aspect of quality management that may not always be apparent from individual deviation records or the administrative status of CAPAs: whether the underlying weakness has been brought under control.

The proposed framework identifies five candidate dimensions: criticality, persistence, recurrence, remediation effectiveness, and interaction and residual risk. Considered together, these dimensions may provide a basis for examining how quality vulnerabilities develop and change during trial conduct.

However, the concept should be considered in the context of existing quality-management systems, which already provide established mechanisms for identifying, investigating and mitigating clinical trial risks. Its contribution will depend on demonstrating that the proposed framework can be defined consistently and provides useful information beyond current quality-management practices.

At present, quality debt remains a conceptual hypothesis rather than a validated metric, regulatory construct or predictor of trial outcomes. Further research should determine whether a structured, longitudinal examination of criticality, persistence, recurrence, remediation effectiveness, interaction and residual risk can improve quality-related decision-making. Ultimately, the value of the concept will depend on whether it provides a clearer understanding of unresolved quality vulnerabilities while supporting the protection of trial participants and the reliability of clinical data.

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