

Optimizing Decentralized Elements in Clinical Trials (DCTs)

TOOL

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Introduction¹

This document is a practical, operational resource intended to help investigators understand the sponsor's role and responsibilities in designing and implementing clinical trials with decentralized elements. An investigator can only calibrate their oversight appropriately if they understand the sponsor's Quality by Design (QbD) approach, including the Critical to Quality (CTQ) factors, relevant to the investigator's role in the trial, the risks to those factors, and the risk mitigation activities already embedded in the protocol. It is intended to translate existing regulatory expectations, such as proportionality, quality by design, and critical-to-quality factors into practical considerations to support study-specific decision-making. It operates within existing regulatory expectations and is not intended to go beyond them.

This is the first document in a two-part series. It addresses the sponsor's role: designing DCT elements into the protocol, identifying critical-to-quality (CTQ) factors, and implementing a proportionate and risk-based approach to quality management into the trial plan. In addition to quality management activities, the sponsor is also responsible for ensuring the infrastructure (e.g., systems, training, data flows) is in place before and during the trial.

The companion document [*Proportionate Oversight Framework for Clinical Trials with Decentralized Elements*](#) addresses the investigator's role: translating the sponsor's risk-based framework into calibrated, site-level oversight. Readers working through both documents will find that the risk-based framework, including the CTQ factors, risks identified, and mitigation activities built into the protocol in this first document serve as direct input for the oversight calibration framework described in the second.

The sponsor bears primary responsibility for the design of the clinical trial and its decentralized elements: selecting appropriate technology; mapping data flows; designing, implementing, and managing strategies to mitigate risks to and protect the CTQ factors throughout trial conduct, and ensuring that sites have the training and infrastructure needed to conduct the trial remotely and conduct it safely and reliably. As a part of its quality management plan, the sponsor should identify risks that may have a meaningful impact on CTQ factors prior to trial initiation and throughout trial conduct. Risks should be considered across the processes, systems, and technologies used in the clinical trial (e.g., trial design, participant selection, informed consent process, randomization, blinding, investigational product administration, data handling, and service provider activities). The sponsor will implement mitigation strategies for risks that they identify and are able to address centrally. The sponsor's activities are important inputs for the investigator to know and integrate into their own oversight strategies.

¹**Note:** This tool is offered as a helpful guide and resource. We would appreciate comments and suggestions to improve its clarity, comprehensiveness, and utility. Please send any comments to MRCTCenter@bwh.harvard.edu.

An investigator who knows that a particular risk has already been mitigated through a protocol-specified control can focus their oversight energy elsewhere, while an investigator who is unaware of those mitigations may either duplicate effort or assume a level of residual risk that does not reflect what is actually in place. For example, if the sponsor has identified blinding integrity as a CTQ factor in a trial where investigational product (IP) is shipped directly to participants and has mitigated that risk through specific packaging and dispensing procedures, or has identified home-based IP administration as a CTQ factor and mitigated the risk of administration error by requiring video-observed administration by a trained home health nurse, the investigator's oversight of those activities looks very different than if no such mitigations were in place.

A critical distinction runs throughout this document: while both sponsors and investigators have corresponding trial oversight responsibilities, the sponsor focuses on trial design and quality management (including risk management and monitoring), whereas the investigator is responsible for trial conduct and oversight for participants for whom they are responsible. The sponsor is responsible for overall quality management of the trial, which includes risk management (e.g., risk identification, evaluation, control, communication, and reporting), and oversight (e.g., quality assurance and quality control activities, including audits and monitoring), as defined in ICH E6(R3). The investigator's obligation is oversight of delegated activities wherever they occur (i.e., performed at the site or conducted remotely), reviewing safety signals, ensuring protocol compliance, and escalating issues to the sponsor, including when the investigator is not sure whether controls are working.

These are distinct and non-interchangeable responsibilities. Only the investigator can delegate tasks that fall within the investigator's responsibility, and the investigator retains oversight of those delegated tasks regardless of who performs them. When a sponsor contracts (or engages) a service provider to conduct an activity (such as home nursing) that falls within the investigator's responsibility, the sponsor is responsible for selecting trained and qualified service providers and ensuring they fulfill the terms of their contract, while the investigator remains responsible for overseeing the trial-related activity as it pertains to the participants under their care. (e.g., ensuring they are conducting the activity as specified in the protocol and reviewing the data and records produced to ensure participant protections and compliance with regulatory requirements.) This is consistent with ICH E6(R3) section 2.4, which states clearly that the investigator retains oversight responsibility regardless of who arranges or performs the activity.

The sponsor should use their risk assessment to guide the development of all trial plans that carry the trial forward (e.g., data management, monitoring, and quality management plans) with efforts focused on protecting the CTQ factors throughout trial conduct. Once the sponsor identifies and defines CTQ factors, associated risks, and risk mitigation strategies, they should communicate those relevant to the investigator. The investigator should use this information to guide the development of their oversight strategy.

This document describes the sponsor's role in optimizing and mitigating risks of a **DCT element**. The investigator's oversight responsibilities, calibrated to the sponsor's risk management strategy, are addressed in the companion document.

Overview

Emerging evidence shows that the introduction of **decentralized elements into clinical trials (DCTs)** helps improve trial participant access to, enrollment of, and retention in clinical trials; increase representative participation; improve protocol performance; and **reduce the burden of participation** for both participants and providers. DCTs are trials that incorporate trial-related activities—such as assessments, monitoring, and data and specimen collection—at locations beyond traditional clinical trial sites, including participants' homes, local clinics and imaging facilities, and local pharmacies, or through digital platforms and health technologies.

Decentralized trial elements were rapidly adopted across diverse disease settings during the COVID-19 pandemic, with early evidence suggesting minimal **impact on data integrity**.² While interest in DCTs remains high, widespread adoption has been limited, in part due to the operational complexity and planning required to ensure safe and effective conduct, reliable data collection, and appropriate oversight. There is a growing **need for a unified framework** to support the systematic adoption of decentralized trial elements.

The **implementation of DCTs**, however, can be complex and requires **careful planning**.³ Sponsors introducing flexibility and increased optionality in clinical trials must couple this with training and education, buttressed by appropriate, risk-proportionate investigator oversight. The plan should be continually reevaluated to modify processes and procedures as experience grows. Each plan should be tailored to the specific clinical trial ("fit for purpose") and should consider confounding factors (e.g., patient population, study phase, IP, condition under study, etc.). Here, we describe an approach to optimizing DCT elements that minimizes risk to CTQ factors, protects participant safety, and preserves data reliability.

² Unger, J. M., Andrews, H. S., Levit, L. A., McKelvey, B. A., Stewart, M., Canin, B., ... Schenkel, C. (2025). *JCO Oncology Advances*, (2). doi:10.1200/oa-25-00021

³ Chen, J., Di, J., Daizadeh, N., Lu, Y., Wang, H., Shen, Y., ... Lee, H. (2025). *Clinical and Translational Science*, 18(2). doi:10.1111/cts.70117

As described in the [Quality by Design \(QbD\)](#) principles document:⁴

“Quality in clinical trials may be defined as the absence of errors that matter. Trial quality ultimately rests on having a well-articulated investigational plan (e.g., protocol, statistical analysis, and management plans). The trial should have clearly defined objectives and associated outcome measures. However, the likelihood of a successful, quality trial can be dramatically improved through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from the trial.

Proactive, cross-functional discussions and decision-making discussions should occur at the time of protocol development to include **1)** what aspects of a trial are critical to generating reliable trial results and providing appropriate protection of research participants (“critical to quality” [CTQ] factors) and **2)** what strategies and actions are necessary to effectively and efficiently support quality in these critical areas.”

Please consult the QbD principles document for more information. The approach described in this framework depends on the rigorous and thoughtful identification of CTQ factors, which guide important areas of focus for sponsor monitoring and investigator oversight.

This approach is also highlighted in ICH E6(R3), which directs sponsors to adopt a QbD approach, identify critical-to-quality factors and associated risks *for each trial*, and let those CTQ factors and risks guide sponsor quality management of the trial, including monitoring, data management, and oversight decisions.⁵ ICH E6(R3) also advises investigators to apply risk proportionality to their oversight activities.

⁴ Clinical Trials Transformation Initiative. CTTI Quality by Design Project—Critical to Quality (CTQ) Factors Principles Document. June 15, 2015. Available at: [CTTI_QbD_CTQ_Principles_Document.pdf](#). Accessed 21 December 2024.

⁵ International Council for Harmonisation. ICH E6(R3) Good Clinical Practice Guideline. Geneva: ICH; January 06, 2025. Available from: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Preparing for the Introduction of DCT Elements



Study Protocol

Sponsors' responsibilities include creating study protocols that are fit for purpose, well-written, clear, and concise. A protocol is a detailed document outlining the background, rationale, objectives, endpoints, study design, eligibility criteria, research procedures and methods, risks, data collection procedures, and statistical considerations. It is the roadmap for conducting the trial, grounded in sound ethical principles and scientific rigor.

Within the protocol, each test, visit, and procedure is described, and specific instructions are provided for all protocol elements, including those conducted outside the investigator's location.

The protocol document and protocol-related documents should clearly note what decentralized elements are incorporated in the trial (e.g., laboratory assessments may be performed by any certified laboratory center; nursing visit may be performed virtually; history and physical may be performed by a local physician provided the data is readily accessible to the investigator) and what (if any) prior approvals or provisions should be in place.



Risk Identification

The sponsor should identify risks that may have a meaningful impact on CTQ factors prior to trial initiation and during trial conduct. Risks should be considered across all clinical trial processes and systems, including computerized systems (e.g., trial design, participant selection, informed consent process, randomization, blinding, investigational product administration, data handling, and service provider activities).

For each DCT element under consideration, the sponsor should conduct a fit-for-purpose assessment to determine whether the element is appropriate for the specific trial. Risks are present in any form of trial set-up, and their identification, along with sufficient control and mitigation, is what allows for a balanced consideration as to whether such trial designs are appropriate. This assessment should be grounded in the trial's CTQ factors, including the criticality of the data being collected and the risks to those factors. The sponsor should also consider who will perform the decentralized activity and where, whether the tools, technologies, and methods being used are appropriate for the population being studied, what training is required for all parties involved, and what management, including oversight and monitoring, and additional safeguards are needed to protect participants and ensure the reliability of trial results.

While some CTQ factors may appear consistently across trials, their associated risks, relevance, and importance should be evaluated on a trial-by-trial basis. For example, when body weight is used to calculate drug dosing or is a primary endpoint, the sponsor should carefully consider what measurement approach is fit for purpose. In an adult population, a calibrated digital scale with standardized measurement conditions and documented verification procedures may be sufficient. However, in a neonate, the same measurement would require a fundamentally different approach, both in terms of the precision required and the design of the scale itself. In both cases, it is the criticality of the measurement to the trial's objectives and context of use in the trial that determines the appropriate levels of control and management.

Not all trial activities are amenable to decentralization. Some procedures, such as certain endpoint assessments, screening physical exams, and subjective efficacy and safety evaluations, require in-person execution and cannot be performed remotely.

Consider the following questions, provided as examples, to help determine whether the decentralized elements are appropriate and fit for purpose and whether risks can be sufficiently mitigated:



Eligibility (Inclusion and Exclusion) Criteria

- Can eligibility be done virtually, or is an in-person visit required?
If an in-person visit, can that visit be conducted remotely by an HCP? Are additional risks introduced by conducting the eligibility determination virtually or remotely?
- How precise, specific, or complex are the criteria?
- Can participants and/or HCPs submit information and data virtually to determine eligibility?
- How are critical factors identified, documented, and monitored?

Data

- Which (if any) critical data points can be collected remotely (e.g., by home health nurses or HCPs, using digital health technologies such as connected sensors, ePROs)?
- Are there risks to participant safety if the data are collected remotely?
- Can sites and participants choose whether they want the visit to be done onsite or remotely? Are risks to data reliability introduced by allowing variability in how the visits are performed? Should all sites and participants adhere to a single method specified in the protocol?

Endpoints

- Are the endpoints quantitative or qualitative?
- Are validated methods for remote data capture to ascertain endpoints available?
- Can trained remote providers be adequately trained to reduce any variability?



Procedures Supporting Study Endpoints and Data Collection

- How necessary is it for these procedures to be conducted consistently or in a highly specific manner or window?
- Is the nature of the interventions/activities to be conducted at remote facilities, and whether any specialized training, personnel, or equipment is needed?
- Should proximity to emergency department be considered dependent on the risk of the interventions?
- Should a pre-qualification check of such facilities by an investigator/sponsor be conducted to ensure suitability?

Investigational Product (IP) Handling and Administration

- Are there specific storage and handling considerations for the IP (e.g., limited stability, restricted distribution product, battery life)?
 - If the risk profile and characteristics of the IP permit shipping, can the IP be shipped to the participant's home, to a local healthcare facility, or to a local pharmacy?
 - If not, must the participant receive it at the clinical trial site? Is there a clearly defined chain of custody as applicable in the geographic jurisdiction?
- What are the specific instructions for the receipt and storage of IP at the participant's home, local facility, or local pharmacy?
- How will the IP be administered remotely?
 - Is a home health nurse or the participant administering the IP?
 - In each case, what training is required?
 - Will the product administration be monitored, and if so, by whom and how (e.g., by a remote video visit)?
- How will the complete, verifiable documentation of the investigational product (and other study items) received, stored, dispensed, returned, and destroyed during a clinical trial be achieved?
- Should there be special sensitivity around time of administration and challenges with undertaking IP accountability?



Participants, Home Health Nurse, and HCP Communication with Study Personnel

- Are clear communication expectations laid out to the HCP?
- Does the participant have access to the internet (e.g., computer, smartphone, internet connectivity), and are they proficient in remote communication?
- Are the digital tools easy to use?
- Are measures required to ensure integrity of the data?

Data Recording and Reporting

- How and by whom will critical data be collected and reported (e.g., CRF, EDC, ePRO)?
- Can IT systems (e.g., EDC, ePROs) be used to send notifications to encourage compliance with the protocol requirements for data capture and reporting?
Can timely reports be made available to the investigator and the site to ensure oversight and continuity of care?



Critical-to-Quality (CTQ) Factors



To protect participants and ensure the reliability of trial results, procedures should be tailored to the importance of the data in the trial and the risks to participant protection and data reliability, as required by ICH E6(R3) and ICH E8(R1). Risks are based on a prospective analysis and ongoing review of critical-to-quality (CTQ) factors to prevent errors that jeopardize rights, safety and well-being and reliable trial results. The principles for QbD, risk proportionality, and quality management are described in these guidelines (ICH-E8⁶ and ICH-E6(R3)⁷), including how to identify CTQ factors.

CTQ factors demand the closest management, including oversight and monitoring, but the risk-proportionate approach should include other study attributes such as safety, data, processes, and systems that have not been identified as CTQ. Routine and ongoing monitoring should be maintained.

Developing a Plan for DCTs

Based on the CTQ factors, each interaction, activity, procedure, and test should then be reviewed to determine whether and how flexibility can be introduced. A sponsor quality management plan and an investigator oversight plan must be in place for every clinical trial. The CTQ factor risk analysis determines not whether a plan should exist, but what that plan should be focused upon, and at what frequency and intensity efforts should be placed on protecting that CTQ factor. Where a trial attribute is identified as critical to quality, both the sponsor's management plans, including monitoring, and the investigator's oversight responsibilities should address it explicitly, with effort proportionate to the associated risk and the robustness of existing controls. Importantly potential risks to a CTQ factor introduced by the flexible or decentralized element do not preclude incorporation of that element in the trial, it simply requires both the sponsor to determine whether appropriate controls to mitigate the risks can be implemented and the investigator to implement appropriate oversight, such that risks that threaten the integrity of the CTQ factor during the conduct of the trial can be identified and can be appropriately controlled.

⁶ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline General Considerations for Clinical Studies E8(R1), Final version Adopted on 6 October 2021, Available at: https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf. Accessed 21 December 2025.

⁷ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline Good Clinical Practice (GCP) E6(R3), Draft version Endorsed on 19 May 2023, Available at: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf. Accessed 21 December 2025.

List of Abbreviations

CRF	Case Report Form
CTQ	Critical-to-Quality
DCT(s)	Decentralized Clinical Trial(s)
EDC	Electronic Data Capture
ePRO(s)	Electronic Patient-Reported Outcome(s)
FDA	U.S. Food and Drug Administration
HCP(s)	Healthcare Provider(s)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IT	Information Technology
QbD	Quality by Design