MRCT CENTER
THE MULTI-REGIONAL CLINICAL TRIALS CENTER OF BRIGHAM AND WOMEN'S HOSPITAL AND HARVARD

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Proportionate Oversight Framework for Clinical Trials with Decentralized Elements

TOOL

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Introduction

This framework addresses investigator oversight—the investigator's responsibility to oversee trial conduct, delegate appropriately, and verify that procedures are executed in accordance with the protocol and applicable regulations. It applies specifically to investigator-level oversight and does not address sponsor monitoring plans or the broader sponsor quality management responsibilities outlined in ICH E6(R3) section 3.10. The proportional approach described here derives from existing FDA and ICH principles, and is not intended to go beyond current regulatory requirements.

This document is intended for trial sponsors, investigators, and other parties who are designing, implementing, and/or overseeing clinical trials with decentralized elements. It serves as a practical decision-support tool for calibrating investigator oversight to the critical-to-quality factors and their identified risks.

This is the second document in a two-part series. The companion document, ***Optimizing Decentralized Elements in Clinical Trials***, addresses the sponsor's responsibilities: designing decentralized clinical trial (DCT) elements into the protocol, identifying critical-to-quality (CTQ) factors, and establishing the quality management infrastructure, including risk management and monitoring. That document highlights the context, the CTQ factors, and their associated risks that make the oversight plan described here actionable and calibrated to risk. That document should be reviewed first.

This document is a practical decision-support tool intended to support implementation of existing regulatory requirements, expectations, and standards, and is not intended to go beyond current regulatory requirements. It aims to translate existing regulatory principles, such as proportionality, quality by design (QbD), and CTQ factors, into practical considerations to support study-specific decision-making. It is intended as a useful, operational resource for trial personnel to support implementation of existing regulatory guidance and ICH guidelines (e.g., ICH E6(R3)) when designing and overseeing clinical trials with decentralized elements.

Overview

Decentralized trials or **trials with decentralized elements (DCTs)** have been described as "those trial-related activities conducted outside the investigator's location. These may include trial visits and/or protocol-related procedures conducted at the trial participant's home, local healthcare centers, or mobile medical units. They also encompass remote interactions, such as video calls or the use of digital health technologies (DHTs) to conduct visits, perform procedures, and collect data."[1] DCTs have an increased reliance on remote procedures and data collection rather than on-site research activities. The introduction of decentralized elements into clinical trials may help improve trial participant enrollment and retention, reduce the burden on participants and their caregivers, and increase representative participation to approximate the populations intended to benefit from the intervention.

In interventional trials, the sponsor[2] is responsible for the overall design and quality management of the trial, including ensuring the rights, safety, and well-being of trial participants and the reliability of trial results. This includes monitoring of trial conduct and oversight of their service providers, while the investigator is responsible for the conduct, safety, and oversight of the trial itself and well-being of the participants under their care. In practice, however, the division of responsibilities can be nuanced; ongoing, timely communication between the sponsor and investigator is critical. Regardless of where, what, and by whom research procedures and data collection occur, however, investigator oversight and sponsor quality management and oversight are necessary to help ensure participant protection and data integrity.

DCT activities can be organized along three dimensions:

- **Who** performs the activity: local healthcare providers (HCPs), home health nurses (HHNs), participants themselves, or their caregivers.
- **Where** it occurs: the participant's home, a local clinical laboratory or imaging facility, a local health-care provider's office or community clinic, or virtually (e.g., telehealth, virtual visits).
- **What** enabling technology is used: digital health technologies (DHTs) such as wearables, sensors, web-based devices, electronic clinical outcome assessments (eCOAs), and other date acquisition tools or computerized systems.

The implementation of DCTs, however, can be complex and requires planning. Any plan to introduce flexibility into, and increase optionality in, clinical trials should be coupled with training, education, and appropriate risk-proportionate investigator oversight.[1] While investigator oversight and sponsor monitoring responsibilities and actions do not differ

between traditional trials and DCTs, here we focus on considerations for those parts of the trial that are performed remotely, considering whether the DCT element will increase risk either by introducing new participant safety concerns or new risks to data quality. The plan for oversight and general trial management and sponsor monitoring should be continually reevaluated to modify the processes and procedures as experience with the protocol (and with DCTs) increases.

This document is based on the following key principles:

- The investigator oversight of the protocol should be focused on critical-to-quality factors and their risks, consistent with the ICH E6(R3) and ICH E8(R1) risk-based frameworks).
- Investigator oversight should be proportionate to the nature of the trial-related activities being performed, the importance of the data being collected, and the risks to trial participant rights, safety, and well-being and data reliability.
- Considerations for determining the level and extent of oversight include the risks of the intervention; the characteristics of the enrolled population and other trial characteristics, investigational product, data sources, the site location, experience, and support; available human, clinical, digital, and financial resources.
- Decentralized elements should first be considered individually and then reevaluated collectively with appropriate weighting of the likelihood and impact of the risk.
- Data paths should be visualized (e.g., through a Data Flow Diagram) to identify potential risks or failure points and define accountability at each transfer point.

[1] ICH E6R3 Annex 2

[2] Here, we will use the term 'sponsor' to mean both sponsors and individuals who serve as sponsor-investigators. A sponsor is the individual, company, institution, or organization that takes responsibility for the initiation, management, and arrangement for financing of a clinical trial but does not actually conduct the trial. A sponsor-investigator, however, both initiates and conducts a clinical investigation and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. This individual, therefore, has the dual responsibilities of both the sponsor and the investigator.

Proportionate Oversight Framework

Appropriate investigator oversight should be proportionate to the risks to participant protection and the reliability of trial results. Achieving this requires the sponsor to design the trial using a quality-by-design (QbD) approach, identify CTQ factors and associated risks, and implement a quality management strategy to protect those factors throughout the trial life cycle. In identifying CTQ factors, the sponsor should consider trial attributes, including the trial design and objectives, the characteristics of the enrolled population, the critical data required to support those objectives, and risks associated with the investigational product (IP).

The sponsor should address any areas in the protocol to ensure the CTQ factors, and then communicate to the investigator those CTQ factors and associated risks that are relevant to the investigator's scope of responsibility, as the full set of CTQ factors may encompass areas beyond the investigator's purview. These CTQ factors form the foundation for investigator oversight. Because each trial is unique, oversight is not a one-size-fits-all approach. The investigator should develop a nuanced, adaptable strategy tailored to the specific trial, with the dual goals of protecting participants and ensuring data integrity.

Appropriate investigator oversight should be proportionate to the risks to participant protection and the reliability of trial results. Achieving this depends on a sequence of distinct steps. Most start with the sponsor and are then carried forward and adapted by the investigator at the site level:

1. **Identify CTQ factors.** During trial design, the sponsor uses a quality-by-design (QbD) approach to identify the critical-to-quality (CTQ) factors: the trial attributes, procedures, and data points whose failure would materially affect participant protections or the reliability of trial results. This step considers the trial design and objectives, the characteristics of the enrolled population, the critical data required to support the trial's objectives, and risks associated with the investigational product (IP).

2. **Assess the risks to those factors.** For each CTQ factor, the sponsor identifies the risks that could compromise it, along with the likelihood and consequence of failure. A CTQ factor is an attribute of the trial that matters to participant protections and/or the reliability of results. A risk is something that could threaten that attribute.

3. **Determine what mitigation strategies** have already been created, and add more where needed. Some of the identified risks are already covered by existing protocol design, standard practice, or established quality processes. For whatever remains uncovered, the sponsor adds mitigations at the protocol level (study design, procedures, training requirements), the quality management level (the overall quality strategy governing the trial), and the monitoring level (the risk-based monitoring plan), so each CTQ factor stays protected across the trial life cycle.

4. **Communicate to the investigator.** The sponsor communicates the CTQ factors and associated risks that are relevant to the investigator's scope of responsibility, along with the mitigations in place (pre-existing or newly added) at the protocol, quality management, and monitoring levels. The full set of CTQ factors may extend beyond the responsibilities of any one investigator.

5. **Assess site-level risk and gaps.** The investigator layers a site-level risk assessment on top of this, covering the site's own standard processes and procedures, the study team's capabilities and experience, the specific participants enrolled and any accommodations they need, and the trial's decentralized elements. This step checks whether the sponsor's pre-work fits the site's setting. Where it does not, the investigator should engage with the sponsor. It also surfaces any gaps between the mitigations already in place and what the site can execute.

6. **Focus oversight on the gaps.** The investigator's oversight plan should concentrate on the gaps between risks (and identified mitigation strategies) and CTQ factors. The scope and intensity of that oversight should be proportionate to the residual risk that remains once existing mitigations are accounted for, and should stay aligned with the sponsor's quality approach.

The sequence here, CTQ factors, then risk, then existing mitigation, then site-level gaps, then oversight focus, underlies the domain-by-domain discussion later in this document:

The questions and risk examples in each domain follow this logic even when not labeled as such.

Because each trial presents a unique combination of risks and characteristics, the right oversight approach differs from trial to trial. The investigator should build a strategy tailored to the specific trial, with the goal of protecting participants and preserving data integrity.

This framework helps determine the details to include in an investigator oversight plan. It does not extend to the sponsor's monitoring plan, which is likely to be more complex and comprehensive. The investigator should assess risk at the site level. That assessment should weigh the specific context of the trial, the site's standard processes and procedures, and any medical risks specific to the enrolled participants. It should also weigh the complexity of the trial's research procedures, the criticality of the data being generated, and the capabilities and experience of the delegated site staff. Like the sponsor's own risk assessment, this should be an ongoing process, revisited as the trial's actual risks and challenges become clearer.

Sponsors ideally involve investigators early in trial design, drawing on the experience of direct care providers familiar with the population to be enrolled. Among the questions the sponsor will ask, several matter directly to the investigator's own execution and oversight of the trial:

Is the decentralized element critical to quality?[3]

- **If not,** what flexibilities could be encouraged, and what guardrails, if any, need to be in place?
- **If it is** critical to quality:
  - What degree of risk mitigation, with particular emphasis on participant protection and data quality, is necessary and sufficient?
  - What risks to participant protection may be encountered?
  - What risks to data quality may occur?
  - How can these risks be minimized, mitigated, or eliminated?
  - What sponsor monitoring is necessary?
  - How can the investigator provide appropriate oversight to the conduct of the trial involving decentralized elements?

After each decentralized element is considered individually, its interdependence with other elements should be considered:

- Does the CTQ factor impact participant protections, the reliability of trial results, or both? How should the focus or rigor be adjusted? Should the investigator prioritize one or more aspects of oversight?
- Do any elements impact other elements in terms of participant protection or data reliability? If so, how can the additive or synergistic impact be mitigated? What can the investigator do to identify risks to participant protection and data reliability and minimize the impact?
- The sponsor should share its CTQ factor analysis with the investigator so the investigator can provide input, then focus their efforts on the key CTQ factors throughout the conduct of the trial.

The following framework is divided into four sections (Participants, Trial Attributes, Research Site Staff, and Investigational Products [IP]), after which decentralized elements should then be evaluated collectively with appropriate weighting and adjusted if necessary. The following framework helps determine the details and considerations for each topic to include in an investigator oversight plan.

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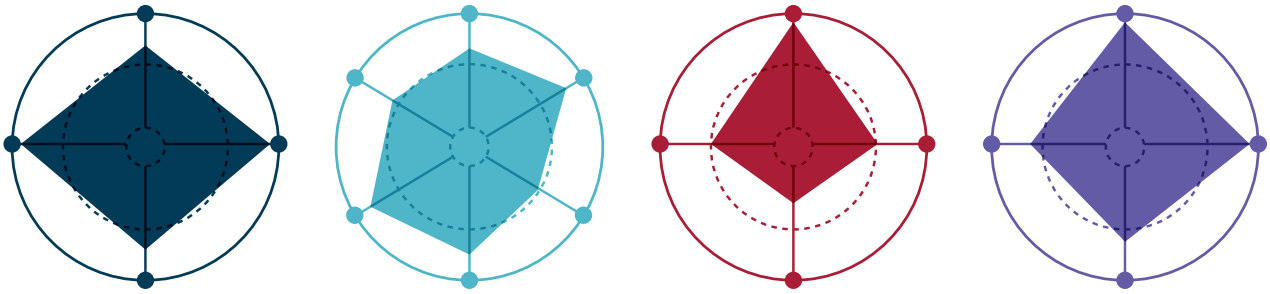
[3] E.g. For more information about the process to ensure that data generated by trials with flexibility are of sufficient quality to provide confidence in the trial results, see Optimizing Data Quality and Flexibility in Clinical Trials project

Major Domains to Consider for Oversight

To optimize comprehensive investigator oversight, **CTQ factors** need to be considered in the context of **four interrelated domains**:



Participants | **Trial Attributes** | **Research Site Staff** | **Investigational Product (IP)**

These icons are meant to be illustrative indicators of the sections in each domain, adjusted as necessary, and not prescriptive.

Each domain is explored in detail in the subsections that follow. Notably, these domains involve some, but not all, of the considerations that sponsors bring to determine CTQ factors and to develop the risk-based quality monitoring (RBQM) plan. The sponsor does this work during planning, considering the study population, study question, IP, and known and potential risks (and what risks can be mitigated or eliminated) to both participant protections and the reliability of trial results. The investigator, then, must translate the knowledge and plan to the individual participant (whose condition may change over time, place, setting, etc.), trial complexity, specific site (e.g., setting, resources, capacity), IP, and other factors that might arise. These factors inform the investigator oversight plan. A solid understanding of the domains will help the investigator to establish, communicate, assess, and revise their oversight plan.

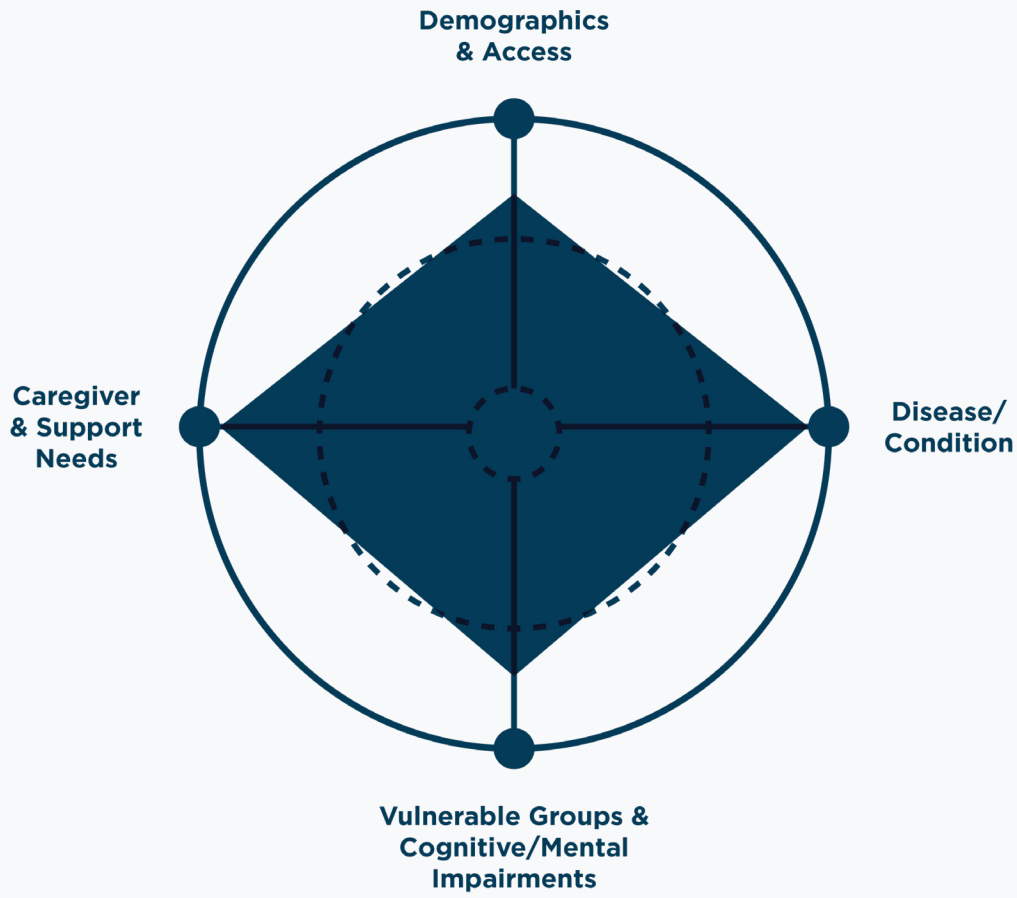
Risks need to be assessed and reassessed during both trial planning and throughout the conduct of the trial. This document uses examples to illustrate risk levels that support decision-making, but actual conditions may change during the trial. Monitoring may show that planned mitigation strategies are less effective than expected, or new risks to safety or data integrity may emerge that were not identified during trial planning. In addition, a factor (or trial attribute) that may not initially seem critical could become a CTQ factor as trial conditions evolve. Likewise, new risks to CTQ factors may also emerge as trial conditions evolve.

The CTQ domains are listed and itemized below. Looking at these domains through the lens of a DCT trial brings out considerations and risks that are more salient in a decentralized setting than in a traditional one. The sponsor communicates the CTQ factors that require investigator oversight. The investigator provides or directs that oversight of the interaction with the participant, wherever and however it occurs.

Below each short domain introduction is a list of questions the sponsor will or will have addressed in planning, which the investigator should appreciate, followed by examples of the CTQ factors at stake in that domain and the risks that can threaten them, generally though not always ordered from lower to higher risk. Consistent with the sequence above, each domain keeps CTQ factors and the risks to them separate. A table entry's position on the risk continuum tells you how severe a risk to a CTQ factor is; it says nothing about whether that item qualifies as a CTQ factor. Neither the questions nor the risk levels and examples are exhaustive.

This document is written for investigators. In each domain section, including its General DCT Oversight Considerations, an action described belongs to the investigator unless it's explicitly attributed to the sponsor. Where sponsor actions appear, they're there for context, so the investigator understands what the sponsor has already done or is expected to do.

PARTICIPANTS



Every participant brings a distinct set of demographics, disease trajectory, vulnerability, and caregiver support, and that profile determines how well suited decentralized elements may be. The considerations below help the sponsors calibrate investigator oversight to the population to be enrolled.

PARTICIPANTS

The sponsor and investigator should consider participant characteristics in their oversight considerations applied to the critical to quality factors identified.

Demographics & Access

- Location—well-resourced versus digital and healthcare resource deserts
- Socio-economic and cultural considerations
- Health and technology literacy
- Resources—knowledge of and access to available healthcare resources

Disease/Condition

- Frequency/incidence (rare vs. common)
- Stability (transient, remitting, fluctuating, stable, progressive)
- Duration (chronic vs acute)
- Severity (benign, life-limiting, life-threatening)
- Mobility status (e.g., ease of traveling)
- Comorbidities and disabilities
- Disease trajectory and exacerbation patterns

Vulnerable Groups & Cognitive/ Mental Impairments

- Vulnerable or special populations (children, elderly, those under legal guardianship, wards of the state, or others for whom additional consent or assent requirements apply)
- Mental health and/or cognitive capacity

Caregiver & Support Needs

- Caregiver involvement and capabilities
- Environment support
- Cumulative caregiver burden from DCT activities

PARTICIPANTS

General DCT Oversight Considerations for Sponsors and Investigators Subsections

- Establish strong communication pathways between the investigator, site personnel, healthcare providers (HCPs), home health nurses (HHNs), and participants and their caregivers to support participants throughout the trial duration.
- Provide access to training and support for participants and caregivers on ePROs, sensors, and digital tools, adjusted to literacy and experience levels, with refresher opportunities and 24-hour technical and emergency assistance. Training and support may be provided directly by the investigator or indirectly through the sponsor or their service providers. However provided, the investigator provides oversight of adequacy, sufficiency, and comprehension.
- Make support materials (guides, quick-reference cards, troubleshooting resources) consistently available (24/7) to participants and caregivers in appropriate languages and formats.
- Implement investigator proportionate oversight (i.e. exploratory endpoints may need less frequent review while primary endpoints need more attention), with sponsor support, and proportionate follow-up (with or without intervention) for triggers related to missing, delayed, or abnormal laboratory, PRO, ClinRO, sensor, and any other data captured remotely. While the sponsor may provide the information, the investigator is responsible for ensuring that the participant receives them.
- Continuously assess whether the DCT approach is appropriate for each participant and participant subgroup: for some populations, decentralized elements reduce risk (e.g., travel burden for mobility-impaired participants); for others, they increase it (e.g., cognitively impaired participants navigating complex instructions or technologies); assessment is dependent on how important the data is.

1. Demographics & Access

Questions to Consider

- Do participants have reliable broadband, digital literacy, and technical ability?
- Are there language or cultural barriers to participation?
- Is healthcare access limited by geography or socioeconomic status?
- Are there age-related digital literacy differences that affect DCT tool use (e.g., pediatric trials involving parent/caregiver interface, geriatric populations with different digital access challenges)?

Risk and Examples

- Urban areas with good healthcare access/broadband coverage
- High health literacy and familiarity with digital tools
- No language or cultural barriers
- Adequate HCP/HHN/broadband coverage
- Suburban or semi-rural settings with inconsistent infrastructure
- Rural areas with limited access to care and resources
- Cultural, financial, language barriers
- Access challenges to healthcare or access to mechanisms of remote communication
- Low to basic health literacy and limited experience with digital health tools—Broadband deserts

Specific DCT Oversight Considerations

- Support participants, caregivers, with sponsor-provided provisioned devices, as necessary.
- Identify challenges with literacy, technology, or connectivity and provide access to alternative solutions.

2. Disease/Condition

Questions to Consider

- Are participants healthy volunteers, or do they have the disease or condition under study?
- What is known about the diagnosis, course, stability, variability, and severity of the disease or condition?
  - Is the disease or condition acute, progressive, remitting, intermittent, or chronic?
  - Is the trajectory of the disease or condition predictable or variable?
  - What is the severity of the disease or condition?
- Does the condition affect the participant's ability to use DCT tools (e.g., tremor affecting touchscreen use, visual impairment affecting app-based ePROs)?
- What real-time oversight is needed to ensure safety?

Risk and Examples

- Healthy volunteers
- Participants with stable chronic diseases or conditions
- Participants with comorbidities
- Participants with progressive conditions
- Participants with conditions that require regular active monitoring

Specific DCT Oversight Considerations

For conditions that limit a participant's ability to interact with DCT tools, the sponsor provides alternative data capture modalities, such as voice-based ePROs, simplified interfaces, or caregiver-assisted data entry, and assesses their success, fidelity, and comparability. The investigator's role is to make the appropriate alternative available to the participant, provide whatever training and support they need to use it, and confirm the modality still fits as the participant's condition changes.

3. Vulnerable Groups & Those with Cognitive/Mental Impairments

Questions to Consider

- Do participants belong to vulnerable populations (children, elderly, disability, participants under legal guardianship, wards of the state, or others for whom additional consent requirements apply under local regulations)?
- Do participants have cognitive or mental health conditions requiring additional support?
- To what extent are caregivers required? Has the reliability of the caregiver been assessed? Is the DCT element structured to accommodate caregiver input, assistance, and/or data?

Risk and Examples

- Healthy Volunteers
- No known vulnerabilities, stable mental health, no cognitive impairments
- Participants with no or minimal comorbidities; independent with no caregiver needs
- Participants with moderate vulnerabilities who require additional considerations
- Comorbidities or vulnerabilities that require management but do not significantly impede participation
- Mental health or cognitive impairment and people with disabilities such that additional support is needed
- Particularly vulnerable participants with specific needs or legal protections
- Participants with multiple severe comorbidities that could impact trial outcomes

Specific DCT Oversight Considerations

- Consider what accommodations and protections are in place for legally protected or particularly vulnerable participants (e.g., children, elderly, those with cognitive impairment).
- Assess caregiver involvement and reliability early and clearly define their role in supporting participant understanding, visit coordination, and data collection.
- Implement additional assessments or check-ins for participants with cognitive or mental health impairment or fluctuating disease status to identify issues promptly.
- Develop and communicate a clear plan to facilitate access to acute care when necessary.
- Increase communication frequency between the site, participant, and caregivers proportionate to the level of vulnerability and variability.

4. Caregiver & Support Needs

Questions to Consider

- What is the expected level of caregiver involvement?
- Are caregivers trained and supported in their role?
- Does the protocol require caregiver-led tasks (e.g., IP administration, monitoring)?
- What is the cumulative time and burden on caregivers introduced by DCT activities; is the caregiver willing, able, and reliable; and does it risk or ameliorate caregiver fatigue or dropout?

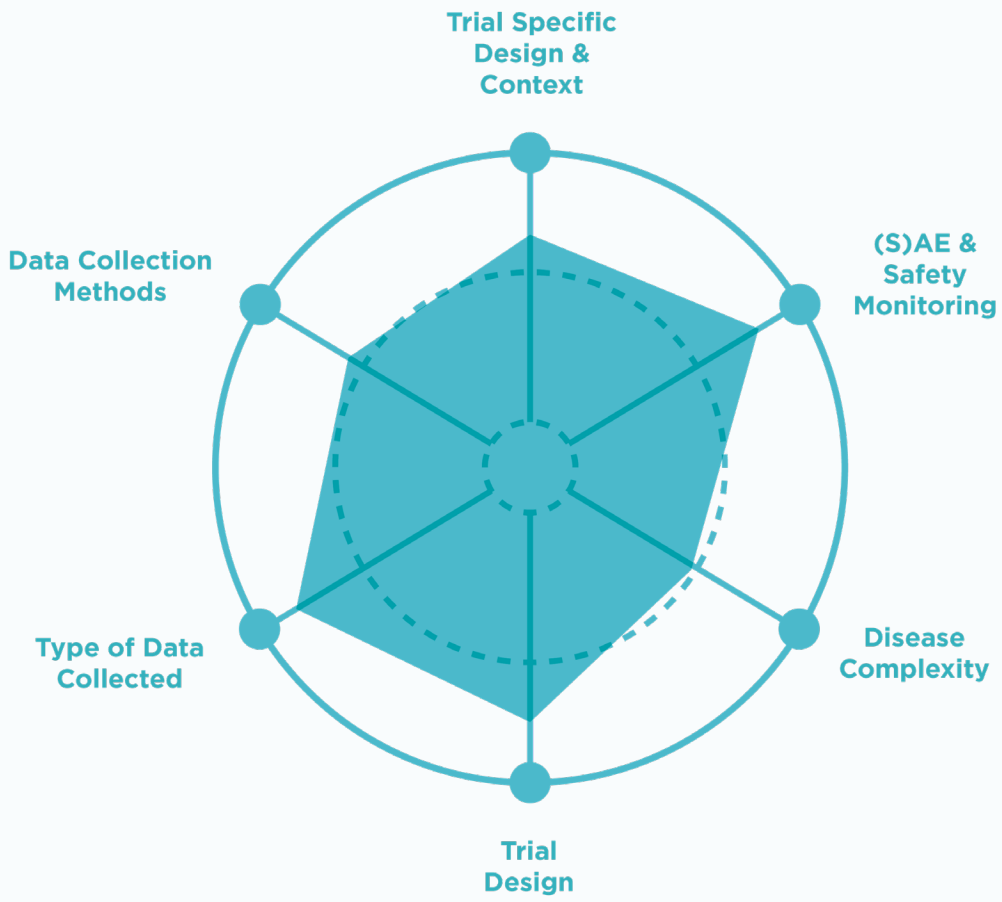
Risk and Examples

- No caregiver needed; Participant fully independent
- Minimal support: occasional help with reminders or technology
- Occasional caregiver assistance for support (e.g. transportation, support, anxiety, depression)
- Routine support; participants relying on care-givers for daily activities and decision-making
- Caregiver regularly assists with devices or ePROs (e.g., cognitive impairment, children, elderly, people with disabilities)
- Critical caregiver tasks; caregiver performs key protocol-required tasks
- Concerning or inconsistent caregiver capacity that may affect safety or data quality

Specific DCT Oversight Considerations

- Provide clear instructions to caregivers proportionate to the study tasks, devices, ePROs, and visit expectations in relation to primary, secondary, and exploratory endpoints.
- Assess caregiver capacity early and confirm understanding of responsibilities before study start. Continue assessment during study as participant condition changes with associated changing caregiver needs and demands.
- Offer dedicated technical support and resources to caregivers, especially when they need assistance with device setup, data entry, or remote assessments.
- Monitor for caregiver fatigue or dropout as an early indicator of participant retention risk.

TRIAL ATTRIBUTES



The protocol-specified study objectives and trial design, the disease or condition under study, the intended population, and the study phase will dictate how investigator oversight should be determined by focusing on the critical-to-quality factors.

TRIAL ATTRIBUTES

Key trial considerations by domain:

Trial Specific Design & Context

- Phase of trial and known safety information about the IP or interventions being studied

(S)AE & Safety Monitoring

- Systems for timely identification and response to adverse events and unanticipated problems
- Trigger systems and thresholds

Disease Complexity

- Stability, chronicity, and trajectory of the disease
- Special oversight needs for assessment and reporting unstable or rare conditions

Trial Design

- Attributes of design (double blind, open label, randomized, placebo-controlled, active controlled, adaptive trial design)
- Endpoint assessment requirements (e.g., routine, validated assessments vs. unique, complex assessments requiring training and specific skills)

Type of Data Collected

- Appropriateness, variability, and validity of collection methods
- Training requirements for local profile HCPs, HHNs, participants, and caregivers

Data Collection Method

- Endpoint criticality (exploratory vs. primary)
- Dynamic vs. stable data signals for remote safety data

What measures, processes, and systems are necessary to help ensure appropriate endpoint?

TRIAL ATTRIBUTES

General DCT Oversight Considerations Applicable Across All Types of Trial Subsections

- Develop, test, and maintain remote communication strategies with HCPs, HHNs, participants, caregivers, and others in all decentralized activities. The level and frequency of communications should be proportionate to the trial characteristics.
- Create clinical trial instruction sheets for HCPs, HHNs, participants, caregivers, and others with reference materials, thresholds for communication to site personnel, and escalation pathways.
- Provide proportionate training and clear instructions for HCPs, HHNs, participants, caregivers, and others on proper data collection procedures, reportable events, and the method and associated timeline to contact research site personnel.
- Establish methods for HCPs, HHNs, participants, caregivers, and others to alert the study team of unanticipated problems or potential safety events.
- Implement systems with clear thresholds to alert study team for timely follow-up and intervention.
- Investigator to develop escalation pathways and document data handling procedures.

1. Trial Specific Design & Context

Questions to Consider

- What are the trial's specific objectives (e.g., safety evaluation, efficacy demonstration, dose-finding)?
- What is known about the IP's safety profile and how does that inform monitoring needs?
- What is the complexity of the trial design (e.g., blinding requirements, endpoint assessments, patient population to be studied)?
- Are there novel operational elements being introduced (e.g., decentralized components, new technologies)?

Risk and Examples

- Broadening eligibility criteria that may increase population heterogeneity
- Complex endpoint assessments requiring specialized training or central review
- Vulnerable or medically fragile patient populations requiring enhanced safety monitoring
- Novel trial designs or first use of specific technologies/approaches

Specific DCT Oversight Considerations

- Implement oversight (e.g., safety monitoring, remote assessments as defined by sponsor) based on trial-specific risk factors, such as:
  - Patient population and medical complexity
  - Novelty of the decentralized approach
  - Complexity of safety monitoring requirements based on known product profile
  - Endpoint assessments and potential for measurement variability
- Trials with established safety data and simpler operational designs may calibrate oversight intensity accordingly, but all trials require DCT-specific planning proportionate to the novelty, context, and complexity of the decentralized approach.
- Investigator oversight strategies should alert to unanticipated signals and communicate concerns and questions to sponsor regardless of trial phase.




2. (S)AE & Safety Monitoring

Questions to Consider

- Are the risks (nature, timing, and severity) of the intervention known?
- What systems are in place to help ensure timely identification, response, reporting and review of adverse events (AEs) and serious adverse events (SAEs)?
- Are processes clear for distinguishing between expected and unexpected safety events?
- What medical and/or emergency services are locally available and are methods to access those services known and communicated?
- How immediate must access to safety data be for investigators and sites?
- Is an escalation pathway from HCPs, HHNs, the research team, or emergency services providers clear and communicated?
- How is consistency assessed in the documentation and response to AEs and SAEs across decentralized settings?
- How will remote data (e.g., sensors, ePROs, telehealth) be captured, transferred, evaluated, and acted upon?
- If emergency unblinding is needed, are processes in place for HCPs, HHNs, or local emergency services to access treatment assignment?

Risk and Examples

- Known safety profile
- Slow onset of AEs
- Later phase trial
- No new combination therapies or comorbidities

*In all cases, consider a monitoring plan for SAEs and detailed instructions for response.

2. (S)AE & Safety Monitoring

Specific DCT Oversight Considerations

- Implement oversight (e.g., safety monitoring, remote assessments) as defined by sponsor for early-phase trials (e.g., first-in-human, Phase I, and some Phase II) that may need additional safeguards (e.g., periodic telehealth check-ins, DHT monitors).
- Late-phase trials (e.g., Phase III, Phase IV) may leverage established safety data to calibrate oversight intensity but still require DCT-specific planning proportionate to the novelty, context, and complexity of the decentralized approach.
- Investigator oversight strategies should alert to unanticipated signals and communicate concerns and questions to sponsor.

3. Disease Complexity

Questions to Consider

- Is the disease or condition stable, chronic, progressive, unstable, acute?
- Is the disease or condition rare?
- Does the disease or condition require special oversight needs?

Risk and Examples

- Stable
- Chronic
- Progressive
- Acute
- Unstable
- Does the rarity of the condition change the risk?

Specific DCT Oversight Considerations

- Stable or chronic conditions may require minimal or no additional specific investigator oversight beyond the general considerations above.
- If a HHN or HCP is needed for disease-specific activities, develop fit-for-purpose training and defined contact and escalation pathways specific to the condition.

4. Trial Design

Questions to Consider

- What are the attributes of design (double blind, open label, randomized, placebo-controlled,active controlled, adaptive trial designs)?
- Are endpoint assessments straightforward or dependent on specialized clinical evaluation?
- Do the design elements require special oversight needs?

Risk and Examples

- Simple design, common procedures, short trial, few visits
- Open-label trial
- Randomized, double-blind trial
- Increasing design complexity
- Complex design

Specific DCT Oversight Considerations

- Simple trial designs (short duration, common research procedures and data collection methods, readily measurable endpoints) may require minimal specialized oversight if standard monitoring and communication practices are sufficient.
- More complex designs (adaptive, long duration, requiring specialized assessments) may require enhanced oversight, including increased investigator visibility, structured communication plans, and tailored remote strategies.
- Remote elements can be implemented in complex designs, provided they are fit-for-purpose and supported by clear documentation and escalation pathways.

5. Type of Data Collected

Questions to Consider

- Are the data sources well validated (e.g., laboratory values, imaging studies FDA-cleared sensors, ePROs)?
- Have the data collection methods undergone User Acceptance Testing by representative participants, caregivers, HCPs, HHNs? Are the graphics and instructions understood?
- What training is required for HCPs, HHNs, participants or caregivers using devices or DHTs?
- How critical are data timeliness and completeness?
- Is the data a primary or secondary endpoint(s) or exploratory?
- Are safety signals expected or possible from the data type?
- How dynamic/critical is the data (stable vs. acute signals)?

Risk and Examples

- Data are generally persistent, reliable, and readily captured (e.g., step count)
- Routine clinical assessments and/or clinically validated (e.g., laboratory) data
- Care providers are collecting data within their scope of practice
- HHNs and HCPs are collecting critical data that needs timely review
- Data collected are dynamic, clinically significant, and/or unpredictable, such as dysrhythmias, ischemic changes, or QT interval in post-MI studies
- Exploratory
- Point in time
- Non-critical
- Accessible by research staff
- Safety signals not expected
- Primary endpoint
- Continuous
- Critical
- Emerging unexpected safety signals possible

Specific DCT Oversight Considerations

- Develop a communication plan for timely reporting of critical or dynamic data to the research site.
- Ensure accurate, complete, and timely capture of primary endpoint and other critical data including safety data.
- Use appropriately rigorous oversight systems proportional to the endpoint criticality (e.g., primary endpoint data requiring stringent and timely oversight and monitoring while exploratory data permitting less demanding oversight.

6. Data Collection Methods

Questions to Consider

- What data collection methods are being used?
- Are the selected methods validated, reliable, and appropriate for the endpoints?
- Do any methods require specialized training or oversight (e.g., early-stage sensors or dermatology televisits)?
- How will data accuracy, completeness, and timeliness be identified, assessed, and reported across decentralized modalities?
- Are clear processes in place for troubleshooting device issues, missing data, or participant noncompliance?
- Do the data collection methods impact safety assessments or require backup procedures?
- Is variability introduced by data collected in remote versus site based entities? What flexibility is permissible and what will compromise data integrity? What choices are available to participant?
- Is the quality and confidentiality of data transfer and storage secured?

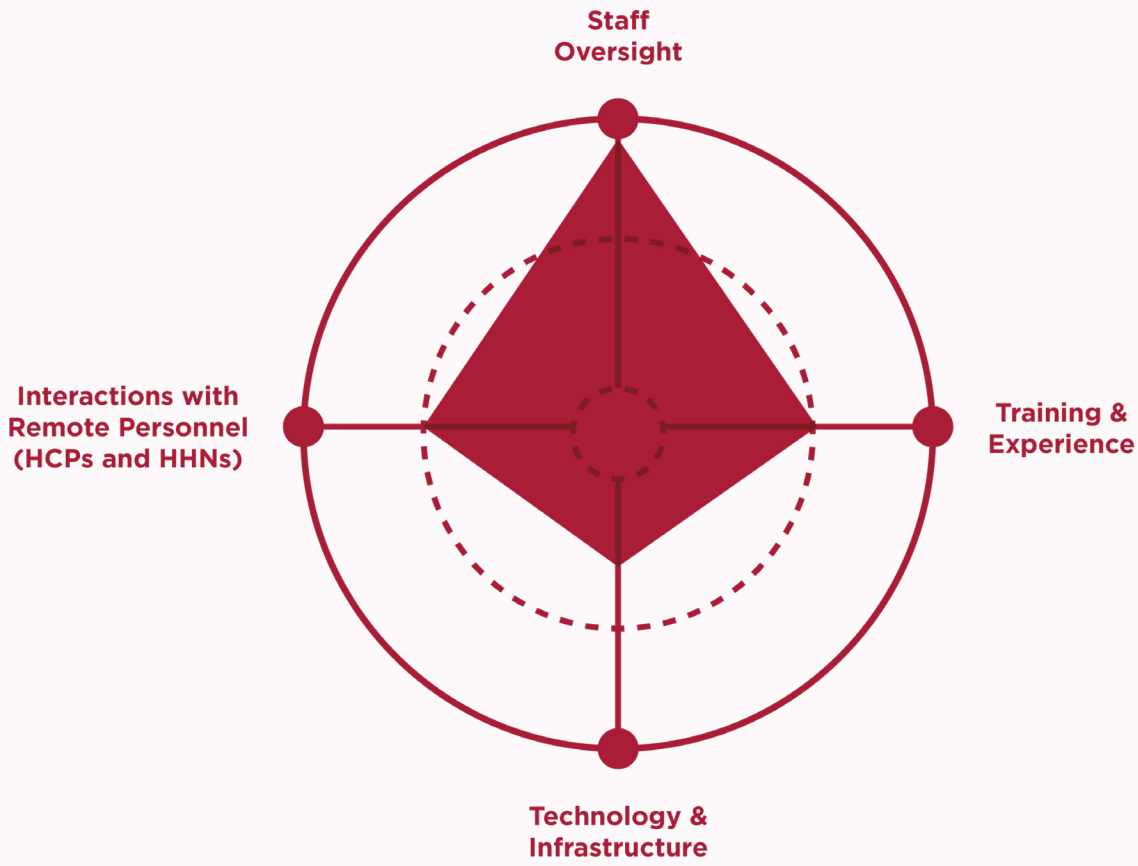
Risk and Examples

- Validated data capture with evidence of accuracy and user acceptance testing
- HHN, HCPs, Laboratory
- Sensors (FDA cleared, good characterization of V3+ (verification, analytical validation, clinical validation, and usability validation)
- Telemedicine/eCOAs
- Sensors Early V3 status or experimental
- Televisit (e.g., dermatology)
- In person at research site

Specific DCT Oversight Considerations

- Use experienced technology vendors with established workflows and support processes.
- Implement a communication and escalation plan for missing, inaccurate, or inconsistent data.
- Monitor sensor and eCOA data for accuracy, completeness, and signal quality; use exploratory devices or early-validation sensors cautiously.
- Avoid relying on experimental sensors for primary safety or endpoint data.
- Maintain standard central site and DCT oversight systems to help ensure data integrity across all collection methods.

RESEARCH SITE STAFF



A site's readiness for decentralized trials depends on its staff's training and experience, its oversight practices, and the reliability of its technology and infrastructure.

The considerations below help the sponsor determine how investigators and their staff may ensure appropriate oversight.

RESEARCH SITE STAFF

Staff oversight, training, and experience may require fit for purpose oversight approaches depending on the condition or disease, technology, DCT elements, and other issues.

Key considerations:

Staff Oversight

- Patient screening and eligibility confirmation
- Treatment protocol adherence
- Adverse event tracking and reporting
- Data integrity verification

Training & Experience

- Prior experience with decentralized elements or digital health tools
- Competency verification and refresher training

Technology & Infrastructure

- Secure, reliable systems for telehealth, remote monitoring, and data transmission
- Fallback/contingency systems and data flow documentation
- System interoperability and integration with DCT platforms

Interactions with Remote Personnel (HCPs and HHNs)

- Identity, credentialing, and competency verification
- Scope of practice confirmation
- Documentation of tasks
- Explicit escalation pathways

RESEARCH SITE STAFF

General DCT Oversight Considerations Applicable Across All Site Staff Subsections

- Provide proportionate training for all staff and remote personnel on decentralized trial procedures, digital tools, and data collection systems in relation to the endpoints before study start, with documented competency assessments.
- Communicate escalation pathways clearly to all research staff, HCPs, and HHNs.
- Outline expectation for staff to complete regular refresher training to maintain competency and address system updates.
- Document training completion, competency assessments, and credentialing for compliance and audit readiness.
- Provide staff for participant tech support and/or to direct participants to the appropriate resources.

1. Staff Oversight

Questions to Consider

- How are patient screening, eligibility checks, protocol adherence, and AE tracking verified?
- Can these be reliably performed remotely?
- What safeguards should be implemented to verify identity and data integrity?

Risk and Examples

- Remote patient screening & eligibility confirmation
- Remote treatment & protocol adherence
- Remote AE tracking and reporting
- In-person by research personnel

Specific DCT Oversight Considerations

- Ensure staff have systems (such as multi-factor identification) to verify appropriate participant enrollment.
- Implement standardized remote screening protocols with clear decision trees.
- Assess usability and understanding of systems that assess data completion and follow up in case of low compliance.
- Provide access to secure video conferencing capabilities for staff to conduct remote oversight activities.
- When trigger notification systems are used, ensure site has the competence and ability to intervene with monitored wearables and ePRO data in a timely manner.

2. Training & Experience

Questions to Consider

- Do staff have prior experience with decentralized elements or digital health tools?
- Based on specific staff responsibilities, what training is needed and how will competency be assessed?
- How frequently should retraining or follow-up occur?

Risk and Examples

- Site research staff are very experienced in disease areas and with trials with remote data capture
- Staff have moderate experience with remote data capture, decentralized trials, but in a new therapeutic area
- Staff is not experienced with trials with decentralized elements

Specific DCT Oversight Considerations

- Communicate clear expectations and document understanding of staff responsibilities in DCTs, including the use of telehealth, wearable devices, and ePRO platforms. Provide asynchronous training opportunities, checklists, tools and other opportunities.
- Assign mentors or support for less experienced personnel.
- Calibrate training intensity to the gap between staff experience and trial requirements—a new therapeutic area for experienced DCT staff requires different training than a first DCT trial for the site.

3. Technology & Infrastructure

Questions to Consider

- Do sites have secure, reliable systems for telehealth, remote monitoring, and data transmission?
- Are fallback/contingency systems in place?
- How is data flow documented and audited?
- Do the site's existing systems (EDC, CTMS, IVRS) integrate with DCT platforms, or are manual data reconciliation steps needed?

Risk and Examples

- Staff technology literacy
- System reliability
- Integration challenges
- Data integrity and security
- Regulatory compliance

Specific DCT Oversight Considerations

- Provide clear SOPs for research-required procedures, telehealth, devices, and data management specific to the technology stack in use.
- Provide site staff with approved backup methods (e.g., paper) for digital technologies and telehealth visits necessary for system failures or downtime.
- After sponsor documents that a site maintains secure, encrypted systems with access controls, the investigator should make schedule regular security audits.
- Where manual data reconciliation between systems is required, implement verification checks to prevent transcription errors.

4. Interactions with Remote Personnel (HCPs and HHNs)

Questions to Consider

- What clinical activities are HCPs and HHNs performing on behalf of the research site (e.g., vital signs, blood draws, ECGs, IP administration, physical and other assessments)?
- Are HCPs and HHNs operating within their professional scope of practice for the trial-specific activities assigned?
- How are HCP and HHN research task assignments documented, communicated, and compensated?
- What mechanisms exist for the investigator and site staff to maintain real-time or near-real-time visibility into activities performed remotely?
- How are protocol deviations, adverse events, or safety concerns identified and escalated when they occur at a remote location?
- What identity verification and credentialing processes are in place for HCPs and HHNs?

Risk and Examples

- HHN collects routine vitals or delivers pre-packaged oral IMP for a well-characterized product in a stable population
- HCP performs protocol-specified clinical assessments (e.g., dermatology photography, neurological exam) that feed directly into endpoint data
- HHN administers injectable IP at home with monitoring requirements
- HCP performs procedures requiring immediate access to emergency provisions

Specific DCT Oversight Considerations

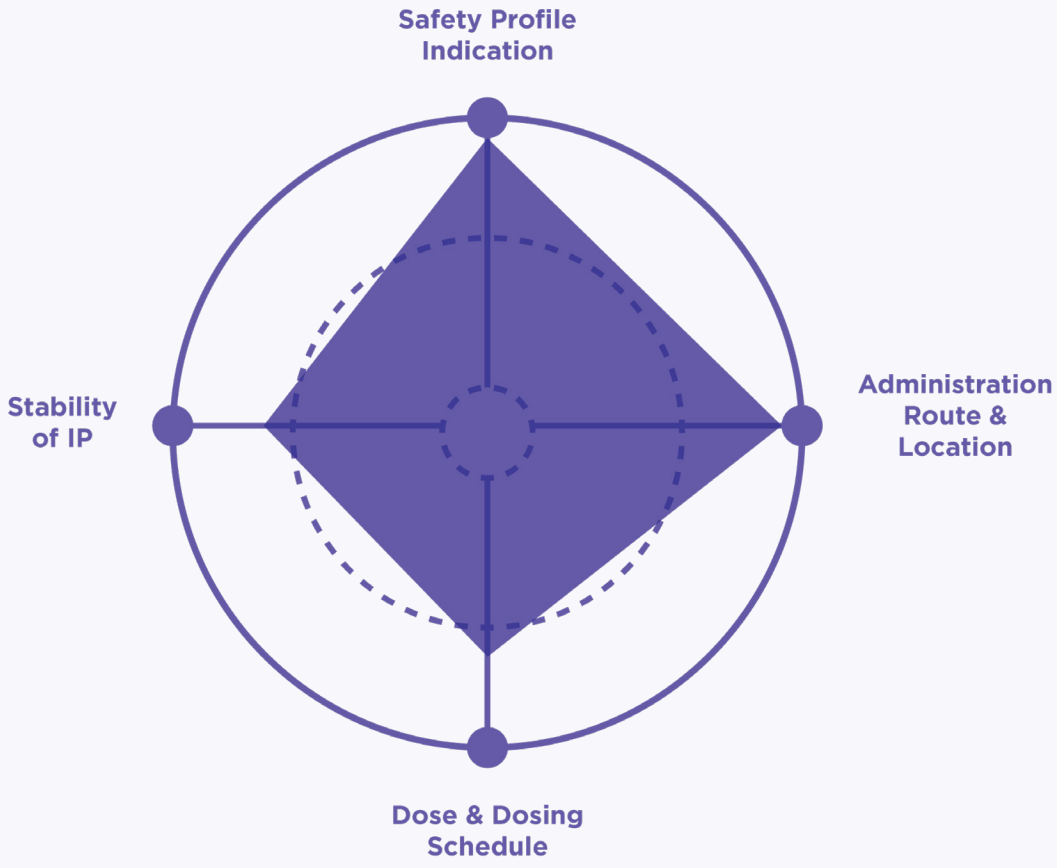
continues on the next page >

4. Interactions with Remote Data Capture Personnel (HCPs and HHNs)

Specific DCT Oversight Considerations

- Provide specific training to address the protocol, the IP, relevant safety signals, and documentation requirements, consistent with HCP and HHN scope of practice.
- Implement credentialing and competency verification before any remote personnel begin protocol activities, with documented sign-off.
- Define, assign, and communicate specific tasks aligned with the investigator's delegation of authority.
- Establish structured communication channels (e.g., secure messaging, scheduled check-ins, real-time dashboards) between the research site and remote personnel.
- Create standardized documentation templates for remote activities so that data captured by HCPs and HHNs is consistent with site-collected data.
- Define explicit escalation pathways for safety events, protocol deviations, and equipment/technology failures encountered during remote visits.
- Consider video-observed procedures for higher-risk activities to maintain investigator oversight without requiring in-person presence.

INVESTIGATIONAL PRODUCT (IP)



IPs are not uniform, and different characteristics can influence the way investigator oversight should be organized. The following are concepts one might consider when evaluating whether IP could be amenable to the flexibilities of a DCT.

INVESTIGATIONAL PRODUCT (IP)

Key considerations by domain:

Safety Profile Indication

- Extent of knowledge of and familiarity with the IP
- Predictability of adverse events

Administration Route & Location

- Administration: Self-administered, HCP/HHN-administered, or site-administered
- Training and supervision requirements

Dose & Dosing Schedule

- Standard vs. complex dosing
- Therapeutic window and monitoring needs

Stability of IP

- Storage requirements and shelf life
- Chain of custody in decentralized setting

General DCT Oversight Considerations Applicable Across All IP Subsections

- Provide clear instructions to participants, caregivers, HCPs and HHNS, for handling, storage, administration, and disposal.
- Where HHN or HCP involvement is needed, develop fit-for-purpose training, engagement strategies, communication plans, and contact plans.
- Instruct prompt reporting of participant symptoms to the study team, whether by participant, caregiver, HHN, or HCP.
- Calibrate the level of oversight proportionate to the proportionate CTQ assessment, risk profile of the IP, and the complexity of the task.

1. Safety Profile Indication

Questions to Consider

- Is the investigational product (IP) well studied, a known drug in a new indication, or does it represent a first-in-class, first-in-human, or a cell or gene therapy?
- How predictable is the safety profile in this indication?
- How predictable is the safety profile with this form of administration (dose, schedule, route)?
- What types of adverse events are expected, and what is the time course for their appearance?
- Can potential adverse events be monitored and managed remotely?

Risk and Examples

- Well-known product and safety profile used in the same indication ("Me-too" drug, known class, Phase IV)
- Known IP but a new indication or Phase II and Phase III studies
- Psychedelics
- First-in-human
- First-in-class
- Gene therapy

Specific DCT Oversight Considerations

- Use brick-and-mortar or hybrid visits when in-person oversight is necessary for safety.
- Maintain rapid escalation pathways for investigators to respond quickly to emerging or unexpected safety signals.
- Increase monitoring frequency and real-time data review for IPs with less predictable or higher-risk safety profiles.
- Ensure timely completion of staff, HCP, HHN, participant, and caregiver reports, including review of DHTs and eCOAs.

2. Administration Route & Location

Questions to Consider

- Does the IP require specialized preparation prior to administration?
- Is specialized training or supervision required for correct administration?
- Are errors in administration likely to lead to significant safety risks?
- Can the administration be safely self-managed at home?

Risk and Examples

- Oral
- Sublingual
- Nasal
- Ocular
- Otic
- Topical
- Transdermal
- Inhaler
- SubQ pens
- Injection (IM, SQ)
- Intravenous injection
- Continuous infusion
- Intraosseous
- Intrathecal

Specific DCT Oversight Considerations

- If direct supervision by research personnel is needed, consider either video-conferencing or research site administration.
- For unfamiliar self-administration (e.g., inhaler, SubQ pen), provide verifiable monitored training with refresher via telemedicine as necessary.

3. Dose & Dosing Schedule

Questions to Consider

- Is the dose and/or dosing schedule tested and standardized or new?
- Is the dose and/or dosing schedule complex (e.g., dependent on dynamic indicators such as laboratory values, fluid status)?
- Does the IP have a wide or narrow therapeutic window?
- How frequently must participant response or toxicity be monitored?
- Are there risks of missed or incorrect doses?

Risk and Examples

- Standard dosing with a wide therapeutic range, well-tolerated
- Dosing requires monitoring of the correct dose, participant's response, and/or adverse events at home via DHT, telemedicine, or a HHN
- Dosing requires monitoring of the correct dose, participant's response, and/or adverse events at the local HCP office
- Dosing requires complex dosing with a narrow therapeutic window, frequent monitoring for toxicity or overdose at the research site

Specific DCT Oversight Considerations

- For complex dosing regimens dependent on dynamic indicators (e.g., lab values, fluid status), clearly define and communicate the dose-adjustment decision pathway to all involved parties. Conduct regular assessments of compliance with dose and dosing schedule and report any deviations or unanticipated problems.
- If guidance during self-administered doses is needed, consider real-time virtual instructions.
- If live oversight during self-administered doses is needed, consider supervision via telemedicine.

4. Stability of IP

Questions to Consider

- Does the IP require highly controlled storage (e.g., -70°C, protection from light)?
- Does the IP require specialized handling or verification of storage conditions?
- Is the IP stable over time?
- Can the IP be stored at room temperature and in ambient light conditions?

Risk and Examples

- Stable under normal storage conditions with a long shelf life
- Requires specific storage conditions, but re-mains stable with proper handling
- Highly controlled environments: Requires -70 degree freezer; Light sensitive; Rapidly degrading

Specific DCT Oversight Considerations

- For IPs with special storage requirements (e.g., cold chain), provide monitored training on handling and storage verification at the point of use.
- For direct-to-patient IP delivery: document how receipt, storage temperature, administration, and disposal of IP are verified when occurring outside the research site.

Bringing It All Together: Collective Evaluation

After assessing each domain individually, the interdependence and collective impact of all decentralized elements must be evaluated. An element that appears low-risk in isolation may become significant when combined with other factors. This section provides a structured approach for moving from individual domain assessments to an integrated oversight plan.

STEP 1: Map Individual Domain Risk Assessments

For each domain (**Participants, Trial Attributes, Research Site Staff, IP**), identify study attributes that are critical to quality, assess the risks to those attributes and the mitigations currently in place, and prioritize oversight efforts where gaps remain and risk is highest.

STEP 2: Identify Interdependencies

Consider how risks in one domain affect or amplify risks in another. For example:

- A complex IP administration route (**IP domain**) combined with low health literacy (**Participants domain**) may require more intensive oversight than either factor alone.
- An early-phase trial design (**Trial Attributes**) combined with inexperienced site staff (**Research Site Staff**) may require enhanced training and more frequent check-ins.
- Remote data capture by HHNs (**Research Site Staff**) for a primary endpoint (**Trial Attributes**) in a vulnerable population (**Participants**) creates compounding risk.

STEP 3: Weight and Prioritize

Not all domains carry equal weight for every trial. Determine which domains and spokes pose the greatest risk for the specific trial, which most impact participant protection and/or data quality, and allocate oversight resources proportionally. Participant protection always takes precedence over data integrity when trade-offs are necessary.

STEP 4: Develop the Integrated Oversight Plan

Synthesize the domain-level assessments into a single oversight plan that addresses:

- Communication pathways between all parties (investigator, site staff, HCPs, HHNs, participants, caregivers)
- Method and timing of documentation between all parties.
- Training requirements across all personnel are calibrated to the specific protocol and proportionate to their role.
- Technology and infrastructure needs, including contingency planning for the decentralized elements deployed.
- Escalation pathways when CTQ tolerance limits are reached.

STEP 5: Plan for Continuous Reevaluation

The oversight plan is a living document. Establish checkpoints to re-evaluate risk assessments as trial data accumulates, as mitigation strategies prove more or less effective than anticipated, and as the operational environment evolves. New risks may emerge; existing risks may diminish. The plan should adapt accordingly.

This collective evaluation should be documented and referenced alongside the Data Flow Diagram (DFD) to provide a complete picture of the oversight strategy. The sponsor will provide the DFD, and the investigator must understand it and provide oversight consistent with it.

The Data Flow Diagram (DFD)

If utilized, the sponsor-generated DFD should visualize the flow of critical data from the point of collection through transfer, processing, analysis, and storage across settings and systems. Following the review and focus on the critical-to-quality factors of the research study, a Data Flow Diagram (DFD) should be included in the protocol, and sponsors should use this framework to determine both whether the data acquisition methods (i.e., people, process, and technology) and tools are fit-for-purpose and whether data management and oversight are adequate.

The **DFD** should:

- Identify all data sources and collection methods
- Map the path of data from generation to analysis to storage
- Highlight critical data points related to primary and secondary endpoints
- Identify potential failure points where data integrity could be compromised
- Define who is accountable at each transfer point for data verification and quality

Sponsor companies and **sponsor-investigators** should evaluate risk levels for data integrity and participant protection and develop a tailored communications and monitoring plan to ensure investigator oversight that includes people, processes, and technology as applicable:

- Establishing and communicating the trial plan with all the involved parties (HCPs, HHNs, etc.)
- Implementing documentation systems
- Identifying indicators of potentially significant events
- Creating contingency plans for potential adverse events and unanticipated problems
- Ensuring ongoing participant education and training
- Ensuring research staff and HCP training and competency verification
- Implementing an escalation plan, including an identified and accountable hierarchy for decision-making.

The investigator interprets the DFD as presented in the protocol. Insofar as the investigator delegates responsibility, the oversight plan should ensure its adequate and timely completion.

For an example of a data flow diagram, see:

CTTI Recommendations for Managing Data

Additional Resources:

CTTI Managing Data Recommendations

ICH E6(R3): GUIDELINE FOR GOOD CLINICAL PRACTICE

FDA Guidance on Conducting Clinical Trials with Decentralized Elements