Session 3: Clinical Trials with Decentralized Elements and GCP Inspections

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Session 3 Introduction

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A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
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Terminology

- Decentralized
- Point of Care (POC)
- Pragmatic

Decentralized

- Some or all trial activities occur at locations other than traditional trial sites, e.g., participants' homes, or local health care facilities
- May involve flexibility – options for where trial activities may occur, e.g. in the setting of contingency planning for disruptive emergencies
- Implementation of decentralized elements in trials increased during the pandemic

Point of Care (POC)/Pragmatic

- Integration of clinical investigations into routine health care
- Use of existing health care infrastructure, e.g., the use of local HCPs to conduct trial assessments
- Use of data collected during routine health care, i.e. RWD
- Simplified protocols with streamlined data collection
- Broad eligibility criteria, may be more reflective of the population intended for the use of a drug
- Facilitated by technologic advances (e.g., electronic medical records, interoperable data systems) that enable integration of clinical studies into routine health care

Decentralized/POC elements

- Does not need to be an all or nothing approach
  - Design elements or set of tools that can be incorporated into trials as appropriate to make trials more efficient and more inclusive
- Overlap between decentralized and point of care elements
  - For example, use of local health care providers to do study assessments

Why?

- Accelerate the development of safe and effective new drugs
- Reliable and generalizable study results in the most efficient fashion, while ensuring participants' protection
- Use of innovative design elements may increase:
  - Efficiency – trial costs and timeframes
  - Generalizability – enrollment of more diverse populations
  - Resiliency – continuing trials during unexpected disruptions to trial operations

Patients/Trial Participants

- Incorporation of these elements may improve convenience and accessibility for participants
- May improve both recruitment and retention of participants
- Participants want convenience and flexibility

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Clinical Trials with Decentralized Elements and GCP Inspections – The US FDA's Perspective

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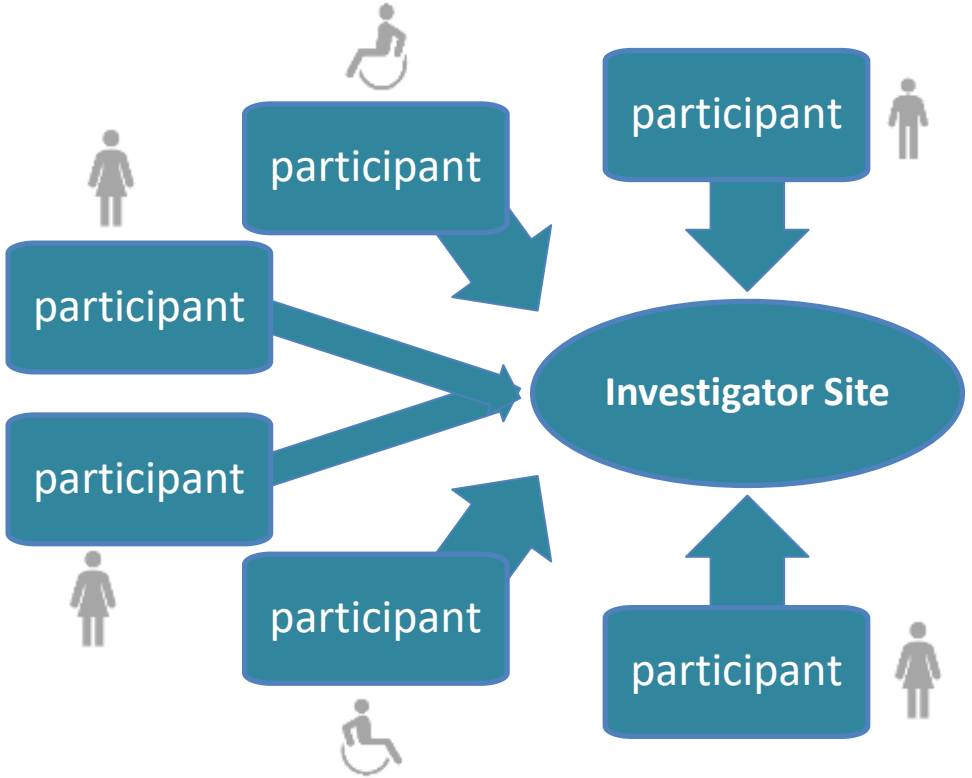
Overview

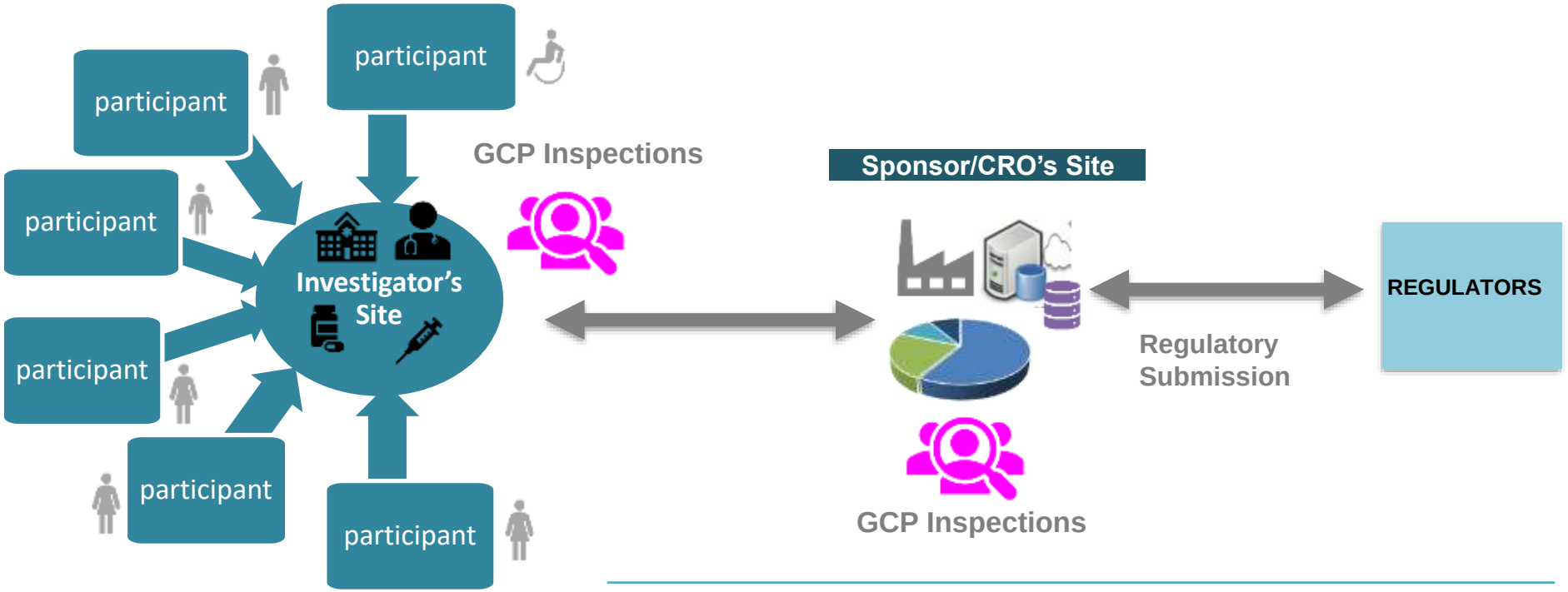
- Brief overview of clinical trials with decentralized elements
- To learn US FDA's regulatory and GCP expectations on trials with decentralized elements

Traditional Clinical Trial Features

- Centered around the clinical trial investigator site
- Require participant travel
- Time-consuming
- Inconvenient, costly
- Restrict access for individuals who live far away from a trial site
- High burden on participants to be enrolled in the trial

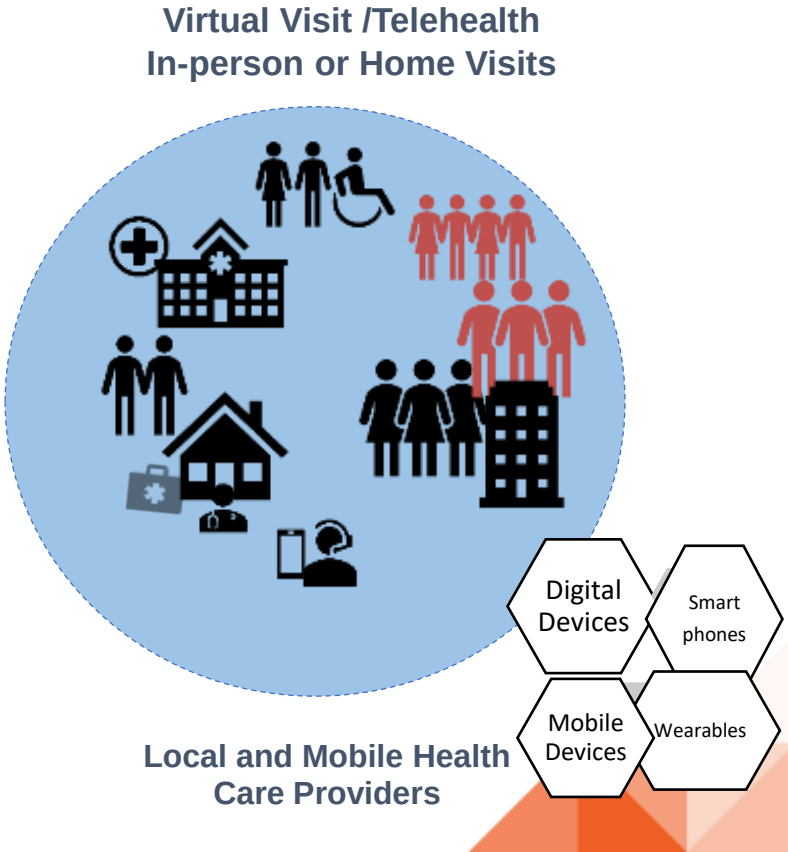


Traditional Clinical Trial Process and GCP Inspections



Trials with Decentralized Elements

- Not centered around clinical trial investigator sites
- Require less participant travel
- Less time-consuming to participant
- Convenient, less costly
- Allow access for individuals who live far away to join trials
- Less burden on participants to be enrolled in the trial



Basis for Use of Trials with Decentralized Elements

- **Public Health Need:** the need to accelerate medical product development requiring new approaches
- **Participants Needs:** better access to clinical trials, convenience and comfort by bringing clinical trials to participants' home or their local health care facilities
- **Industry Needs:** faster improved trial participant recruitment, potential reduction in economic costs, potential increase in diversity of the population in trials
- **Advance in technology:** increase in use of computerized systems such as telehealth and Digital Health Technologies (DHTs), ability to capture data more frequently and efficiently

Determining Appropriateness of a Trial with Decentralized Elements

- Nature of the disease
- Design of the trial
- Geography
- Technology: digital health technologies (DHT), E-platforms
- Endpoint appropriateness
- Trial procedures
- Investigational product storage and administration
- Local health care services
- Compliance with state and regional laws

Considerations for Designing Trials with Decentralized Elements

- Determine which activities must occur at the investigative site, a local or mobile HCP, and which are amenable to remote technology solutions
- Implement additional trial safeguards, processes, training, and/or procedures to ensure participant safety and adequate trial oversight
- Designate where and how local **source documents and electronic information** will be stored
- Ethical principles and the standards for the evaluation of clinical trials by IRBs/IECs for trials with standard design applies to trials with decentralized elements. Particular attention should be given to privacy and confidentiality of the participants and security of data.

Considerations for Designing Trials with Decentralized Elements (cont.)

- Consider regional differences in **remote technology** availability
- Manage **contractual relationships** with non-trial personnel (e.g., local HCPs), facilities (e.g., local clinical laboratories and imaging services), and coordination of the timing of remote visits and procedures.
- Determine **trainings** needed for trial participants and study staff for telehealth visits and use of DHT

Regardless of the clinical trial type, sponsors are encouraged to contact FDA review division early in the planning stages of the trial to discuss feasibility of the data to support a regulatory action

US FDA's Regulatory and GCP Expectations

- Trials with decentralized elements are subject to the **same regulatory requirements** as other FDA-regulated clinical trials.
- FDA's **GCP expectations are the same** for trials with decentralized elements and traditional clinical trials.
- Regardless of the type of clinical trials, the regulatory **responsibilities** of clinical investigators and sponsors/CROs **do not change**.

Sponsors/CROs Responsibilities

- Sponsors/CROs should ensure that digital health technologies (DHTs) are available and suitable for use by all relevant participant populations.
- The use of DHTs should comply with laws governing telehealth in different states and/or countries.
- Given the increased use of computerized systems and the increased complexity of the data flow, it is very important that sponsor ensure adequate and close oversight of trials with decentralized elements

Monitoring

As with any trial, sponsors may use a variety of approaches to monitor trials with decentralized elements, and the monitoring plan should be based on the sponsor's risk assessment of the trial processes/procedures and data (safety and efficacy).

A trial monitoring plan should:

1. describe how monitoring will be implemented to assess protocol compliance and data quality and integrity;
2. specify the frequency with which trial records and source documents will be reviewed; and
3. note any unique aspects related to trials with decentralized elements procedures.

Clinical Investigator's Responsibilities

Clinical investigators in trials with decentralized elements have the same responsibilities as traditional clinical trials

- Conduct and provide oversight of clinical trials
- Select qualified staff for delegation of responsibilities
- Informed consent procedures/IRB approval
- Ensure test article accountability
- Adhere to study protocol and record keeping
- Communicate with monitors/sponsors
- Report adverse events

Delegation of Study Related Functions

- When permitted by sponsors, investigators may delegate others to conduct study-related procedures
- These procedures may take place at participants' homes or at facilities authorized by the investigator
- Investigators should ensure that delegated staff are qualified by education, training, and experience
- Investigators should ensure that data obtained are complete and, that procedures are conducted according to the protocol.

FDA GCP Inspections

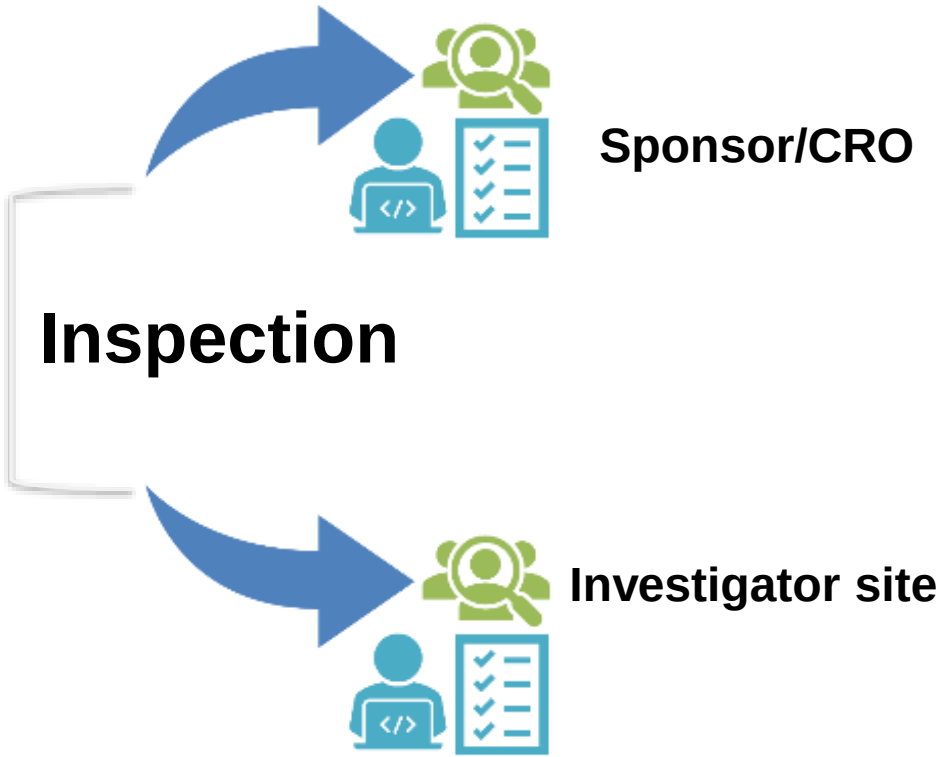
- For trials with decentralized elements the sponsor should provide the location where trials with decentralized elements-related records and source documents are located and accessible and where the investigator and other trial personnel can be interviewed for US FDA inspection purposes.

- Information required under applicable regulations to be maintained for the trial audit should be accessible by FDA inspectors

GCP Inspections of Trials with Decentralized Elements

- Process for conducting inspections is the same for trials with decentralized elements as they are for traditional trials

- Investigator inspections are conducted at a location where trial records and source documents are available or accessible



Summary

- Regardless of the type of clinical trial, the regulatory responsibilities of investigators and sponsors/CROs do not change
- FDA's regulatory and GCP expectations remain the same
- Process for conducting inspections is the same for trials with decentralized elements

Acknowledgement

- Jenn Sellers, MD, PhD
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Trials Incorporating Decentralized Elements

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Overview

- Dialogue with Regulators
- Risk assessment
- ICH guidelines and Decentralized Clinical Trials (DCTs)
- Impact of COVID on development of DCTs
- Regulatory challenges for trials with DCT elements
- Future of DCTs

Dialogue/Early engagement with regulators

- Early planning and designing of the trial, the sponsor should discuss the approach to be used with the Agencies:
  - **MHRA**: Innovative Licensing & Access Pathway (ILAP) / Innovation, Scientific Advice meetings
  - **FDA:** Pre IND (Pre-Investigational New Drug Application) meeting
  - **HC:** Pre-application meeting with the Review Directorates, GCP requirements can be discussed with Compliance & Enforcement Unit

Risk Assessment

- Regardless of the approach, investigator and sponsor responsibilities do not change
- Sponsor and investigator are responsible for risks to the quality and integrity of the study and the data being collected
- Risk Assessment needs to be undertaken by the sponsor and particular risks must be identified

ICH and Decentralized Clinical Trials

No specific ICH guidelines on this topic. However:

- ICH E8(R1) guideline
  - Promotes identification of critical-to-quality factors and focussing on activities essential to the study
- ICH E6(R3) guideline
  - Encourages innovation and is intended to be flexible and modern
  - Development of updates to the guideline are being informed by lessons learned during the pandemic

Impact of the COVID pandemic for DCTs

- The pandemic brought challenges that directly impacted clinical trials:
  - Need to avoid having participants contract the virus
  - Health care resources being diverted to other priorities
  - Need to follow public health recommendations

- Health Canada issued **Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors**

- Acceleration of acceptance of decentralized trials
  - While some aspects still need to be explored, offers opportunities for improved recruitment and diversity

Canada – Main Academic Centers

What is an investigator site and who is responsible for the medical oversight and other GCP Investigator responsibilities

- **Present Definition of Clinical Trial Site:** ***The location where trial-related activities are actually conducted (ICH E6, 1.59).***

Current Regulatory provisions:

- C.05.010(d) for each clinical trial site, the approval of a Research Ethics Board is obtained before the clinical trial begins at the site;
- C.05.010(e) at each clinical trial site, there is no more than one QI;
- C.05.010(f) at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the QI;
- C.05.012(3)(f) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator

- ***Future Definition to reflect the location(s) where trial-related activities are actually conducted under the responsibility of one investigator who is licensed to practice within the physical location where the trial activities are carried out or coordinated by an investigator for the conduct of the clinical trial.***

Future Challenges: Guidance To Clarify

- Activities to be considered safe and suitable for DCTs; examples of the types of off-site locations and how they would be documented (e.g., Clinical Trial Site Information form, protocol, etc.)
- REB approval as REB approval is required for a clinical trial site
- Need to assess potential risks, time and resource requirements to inspect DCTs, and the challenges for DCT sponsors and sites to adhere to GCP
- Sponsor oversight of all Clinical Trial (CT) activities at both the main site and off-site locations
- Sponsors to ensure off-site locations record and handle data appropriately
- Sponsors to ensure off-site locations have staff with the appropriate training and competencies to fulfill duties to protect the health and safety of participants with respect to their participation in DCT
- Investigator to oversee activities at off-site locations including oversight of staff duties and activities related to a CT and the day-to-day practice-of-care
- Enrolment and consenting participants and use of appropriate technologies in DCTs

Remote Informed Consent

- **Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulations:** https://gazette.gc.ca/rp-pr/p2/2022/2022-03-02/html/sor-dors18-eng.html
- **PART 3. General**
- **Remote written informed consent**
  - **36 (1)** If a qualified investigator is not able to obtain, in person, the written informed consent of a person to participate in a clinical trial in respect of a COVID-19 medical device for which a COVID-19 medical device authorization has been issued or a COVID-19 drug for which a COVID-19 drug authorization has been issued, the qualified investigator may obtain the written informed consent remotely.
- **Non-written informed consent**
  - **(2)** In the case where the person is not able to provide their written informed consent, the qualified investigator may obtain their non-written informed consent if the following conditions are met:
    - **(a)** the qualified investigator reads the contents of the informed consent form to the person;
    - **(b)** the person provides their informed consent before a witness; and
    - **(c)** an attestation by the witness that the person has provided their informed consent is provided to the qualified investigator as soon as feasible.

A look at the future

- Upcoming Modernization of clinical trial regulations:
  - Plan is to have a risk-based approach, a more flexible framework
- Updates of ICH E6(R2) will provide additional flexibility in CTs
- DCTs are an option going forward

Thank You!

Questions?

Clinical Trial Compliance Program

E-mail: GCP_BPC@hc-sc.gc.ca

Further information available online at:

www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html

Inspection case studies; Trials involving Decentralised and Innovative Features

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Overview

- What we have seen on inspection
  - 3 inspection case examples
- Are common themes / issues emerging?
- Summary

Decentralised Trials and Trials using Innovative Features

- Some or all trial activities occur at locations other than traditional clinical investigator site.
- Use of digital health technology tools, and other electronic systems (e.g IRTs, ePROs and eCOAs).
- Use of existing healthcare ecosystem and mobile study personnel.
- Integrating aspects of standard clinical practice into the design of the trial (e.g. simplified protocols and streamlined data collection).

Case 1

- Decentralised trial
- Consent was being conducted remotely and documented in a trial specific Electronic Database, set-up by the Sponsor.

Case 1: Consent

- No **written** consent was obtained from the participant/witness.
- Inadequate process for provision of completed ICF to the trial participants.
- No record of PIS/ICF version used at Informed Consent.

Case 1: Consent continued

- No ID check or process to authenticate participants.
- Issues with the process for obtaining consent by a legal representative on behalf of a participant lacking capacity.

Case 2

- Trial involving innovative features i.e. existing healthcare systems; use of registry data for clinical outcomes for primary and secondary endpoints.
- Registry data used alongside eCRF data.

Case 2: Data Integrity Control Processes

- In the analysis datasets, the eCRF data was being replaced with registry data without appropriate processes (lack of queries to amend the eCRF, source data verification and investigator approval).
- This was not detailed in the protocol.

Case 2: Data Integrity Control Processes (2)

- There was no documented detailed assessment of the quality assurance of the registry data by the trial management team prior to use of the data provided.
- It could not be confirmed whether the registry data in all cases would be reliable.

Case 3

- Trial involving DCT elements such as central recruitment and screening with Blood Pressure (BP) monitors shipped to patients to use at home.
- Data completed and submitted by patients using an app.

Case 3: Risk Assessment

- Trial risk assessment did not identify and therefore mitigate key areas of risk, e.g;
  - Risk of capturing patient identifiable information/data in Sponsor Database

Case 3: Risk Assessment (2)

- Trial risk assessment was not updated throughout trial;
  - Substantial amendments
  - Upon identifying significant issues/deviations

Common Themes of Issues - Sponsor

- Risk assessment and reassessment inadequacies
- Participant confidentiality breaches – identifiable data collected in Sponsor systems
- Documentation and verification of activities
  - How can you as auditors or us as inspectors see that oversight was maintained, that processes were followed etc

Common Themes of Issues – Site / Principal Investigator

- Investigator oversight
- Staff delegation & responsibilities
  - PI duties/functions contracted by the Sponsor with no delegation by Investigator
  - Delayed delegation
- Documentation and verification of activities
  - How can you as auditors or us as inspectors see that oversight was maintained, that processes were followed etc

Summary Learnings

- The fundamental rules of GCP can and do still apply whatever the innovative design being used e.g. consent must be documented by participant although a proportionate approach can be taken.
- If innovative and/or pragmatic features are being used, an assessment for appropriateness, compliance and risks should be completed and revisited.
- Risk assessment is key and is not a one-off for the trial.

Closing Thought

Avoid issues by applying ***Quality by Design*** and ensuring a ***robust Risk Assessment*** is maintained throughout.

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