Decentralized Clinical Trials

Oversite and How FDA Reviews

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Overview

Why

Regulations

Potential Tools

Oversight and execution

Design of DCTs

eInformed Consent

Remote Visits

eSource

Remote Monitoring

Guidance

Why?

"Building quality into the design and conduct of trials and encouraging the use of innovative trial designs and health technologies are essential to truly advance clinical trials and generate meaningful results"

-Robert M. Califf, M.D., FDA Commissioner

Why Decentralized Clinical Trials

"Decentralized clinical trials may **enhance convenience** for trial participants, **reduce the burden on caregivers**, expand access to **more diverse populations**, improve trial **efficiencies**, and facilitate **research on rare diseases** and diseases affecting **populations with limited mobility**."

-Robert M. Califf, M.D., FDA Commissioner

Enhancing Participation in Clinical Trials**

- …called on sponsors to reduce participation burden through remote assessments and decentralized or hybrid elements as critical for improving enrollment and retention.

Regulations for Decentralized vs. Traditional Clinical Trials

- 21 CFR 312.50
- 21 CFR 812.40
- 21 CFR 50

… select qualified investigators…provide information to conduct investigation… ensure monitoring … ensure investigational plan and protocol are followed … ensure investigators, reviewing IRBs, and FDA are promptly informed of significant new information …

Regulations: 21 CFR part 11

- Electronic Records
- Electronic Signatures

Defined

- Traditional: Data collected from Subjects at a central location
- Decentralized: Clinical trials using digital technologies to have remote interactions with real participants
- Virtual
  - Pre-clinical trial conducted in simulation or computer models
  - DCT with no in person interactions
- Hybrid: combination of traditional and decentralized methods

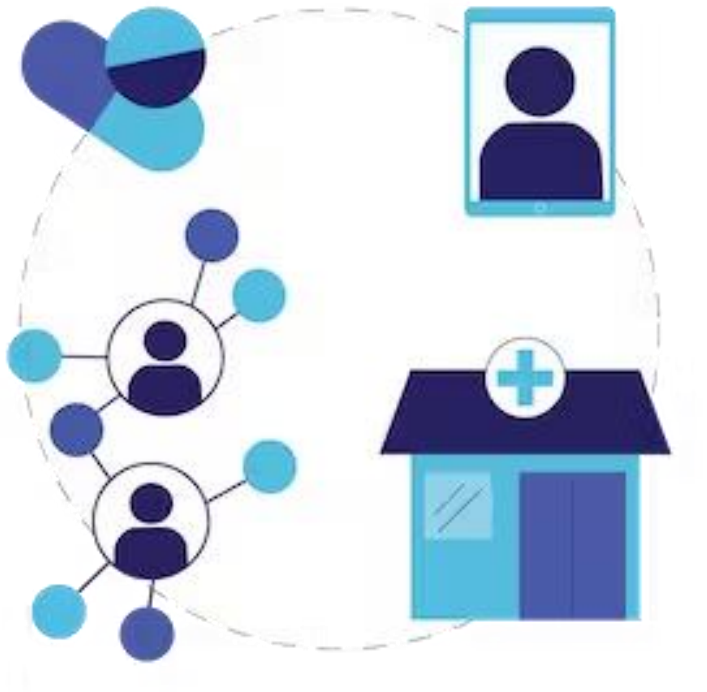
Potential Tools

- Remote Informed Consent
- Local/Home healthcare providers
- Wearables
- Handheld Devices
- Telemedicine
- Investigational Product Shipped Directly to Subjects
- Electronic Clinical Assessments

Perceived/Potential Concerns Decentralized Clinical Trials:

- Immature digital infrastructure
- Privacy concerns
- Limited experience of Clinical Investigator overseeing tools utilized in the trial
- Perception of regulatory barriers
- Variation in state laws and regulations
- Consistency in protocol execution

Designing a Decentralized Clinical Trial



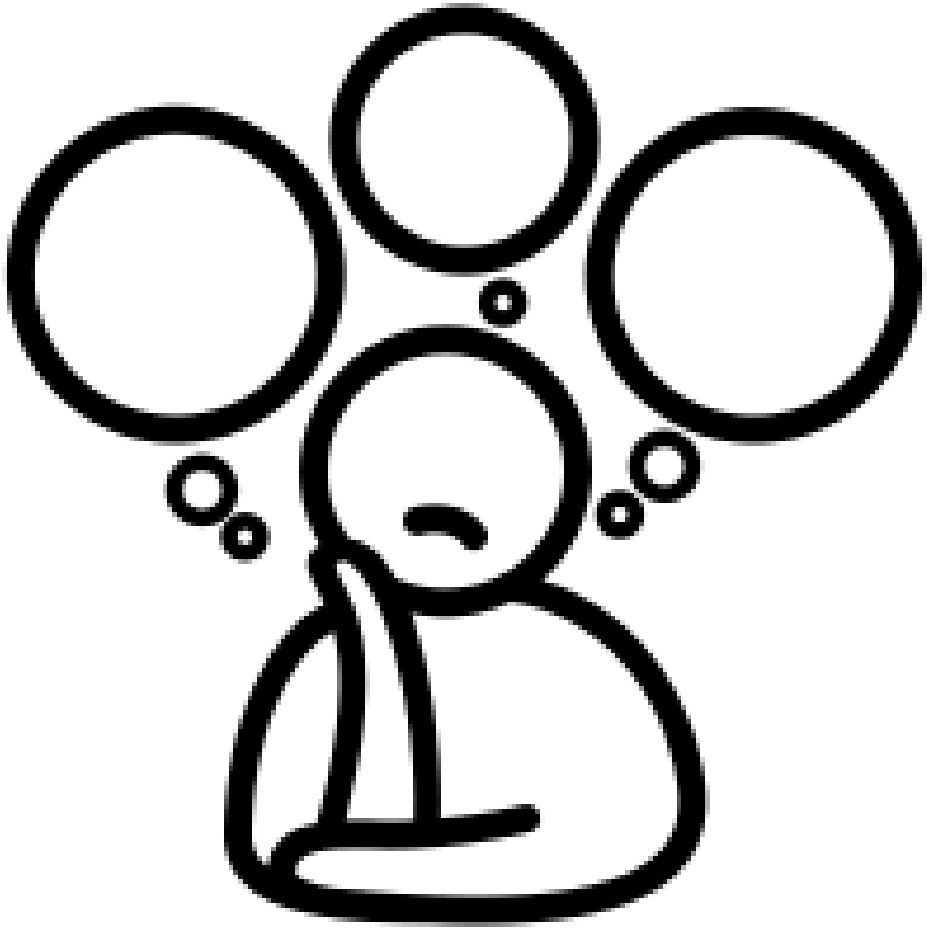
- Does it make sense in the context
  - Inpatient vs. outpatient activities
- Can human subject protections be assured
- How can the quality and integrity of the data be ensured
  - Initial data collection
  - Oversite
  - Monitoring!

Determine Potential Tools

- Evaluate what tools will be used
- Evaluate potential concerns with population
  - Mitigate
  - Change in Method
- How do you ensure the tool works as intended
  - Validation
  - Verification

Oversight and execution of potential tools

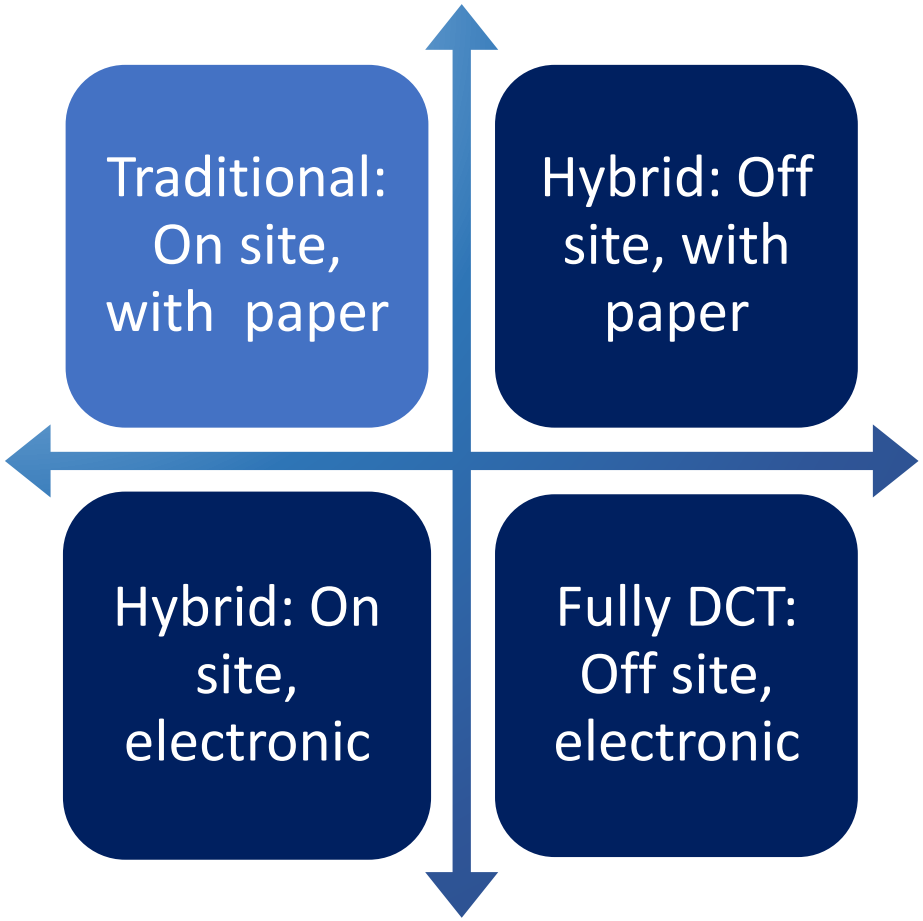
- For each tool used consider
  - What information will be collected
  - How will data be transferred
  - How will the Clinical Investigator access/review/oversee
  - How will the sponsor access/review data
  - What happens when a digital tool is unavailable



Potential Tools

Informed Consent

- Not just a signature!
- A documented dialogue
- Facilitates a potential subjects understanding
- Allows for the subject to ask question and discuss
- Required interaction with qualified/delegated study staff



Remote/electronic Informed Consent Tools

- Paper Form
- Electronic Form
- Embedded audio/video
- Passive or interactive website
- Electronic Messages
- Telephone calls
- Video conferences
- Live Chats
- Combination of methods

Informed Consent monitoring/oversite

- Ensuring who the subject is
  - Visual confirmation
  - Identification
  - How is it documented?
- Ensuring subject read/received the information
  - Electronic –page read times
  - Subject comfortable with format?

Informed Consent monitoring/oversite

- How is comprehension assessed
  - Quizzes
  - Discussion
- Opportunity to ask questions
- Clear documentation of interaction/discussion with Subject
  - NO “terms of service agreement” situations

Local/Home healthcare providers

- Selection
- Who oversees
- How is data collected/submitted
  - Timely communications to overseeing Clinical Investigator
    - Adverse Events
    - Study Visit Data
- Resolving incomplete data
- Ongoing oversite

Local/Home healthcare providers: Real World Concerns

- Clinical Investigators are responsible for oversite but often sponsors hire/select vendors
  - How do Clinical Investigators have meaningful authority/oversite
    - Delegations?
    - Communications?
- We see:
  - Missing information
  - Visit information not sent to clinical site for months
    - Is SAE reporting/care affected
    - AEs
    - Compare source home health records vs. case report forms

Wearables**

- How do you ensure the subject is wearing it
- Who/How is the data accessed
- How frequently is data being monitored
- Wearable adverse events handling
  - E.g. rash from CGM
- What to do in the case of abnormal results
  - Eg. Abnormal heart rhythm
- How is data transferred
  - Rural/no network

Wearables: Reviewing Data

- Access to Source Data?
- Complete?
  - Look at verification data transmissions
  - Source data compared to reporting
- Data Processing?
  - Look at conversions or calculations for accuracy
- Documentation of review of data by clinical site?

Handheld Devices

- Do the subjects know how to use the device
- What happens when failure happen
  - How is the Clinical Investigator Aware
- How is data reviewed/accessed

Handheld Devices: Look At

- Did subjects use the device?
  - Missing data d/t lack of:
    - Protocol required training
    - Device failures
    - Devices not sent to Clinical Site
- Data available?
  - Lost in transmission
  - Not provided to site
  - Verification/validation?

Telemedicine

- Video vs Audio
- Privacy
- Confirming Subject
- Data from visit

Telemedicine: Look At

- When was visit information record
  - Late entries?
    - A few day vs. a month

Investigational Product Shipped Directly to Subjects

- Transport methods
- Temperature monitoring
- Accountability
- Returns

Investigational Product Shipped Directly to Subjects: Look at

- Temperature excursions
  - In temperature logs
  - Alarm records
  - Who reviews excursions
  - When are excursions reviewed
  - Is the clinical investigator aware of excursions
- Shipping records
  - Missing shipments?

Electronic Clinical Assessments

- Who completes
- How is the data transferred
- How is the data reviewed
  - Clinical Investigator
  - Monitor
  - Sponsor

Electronic Clinical Assessments: Look At

- Audit trails
  - Review when data is entered
- Transmission data
  - Can you see where the data come from
- Are questionnaires comprehensive?
  - Review what happens when subjects don't answer questions

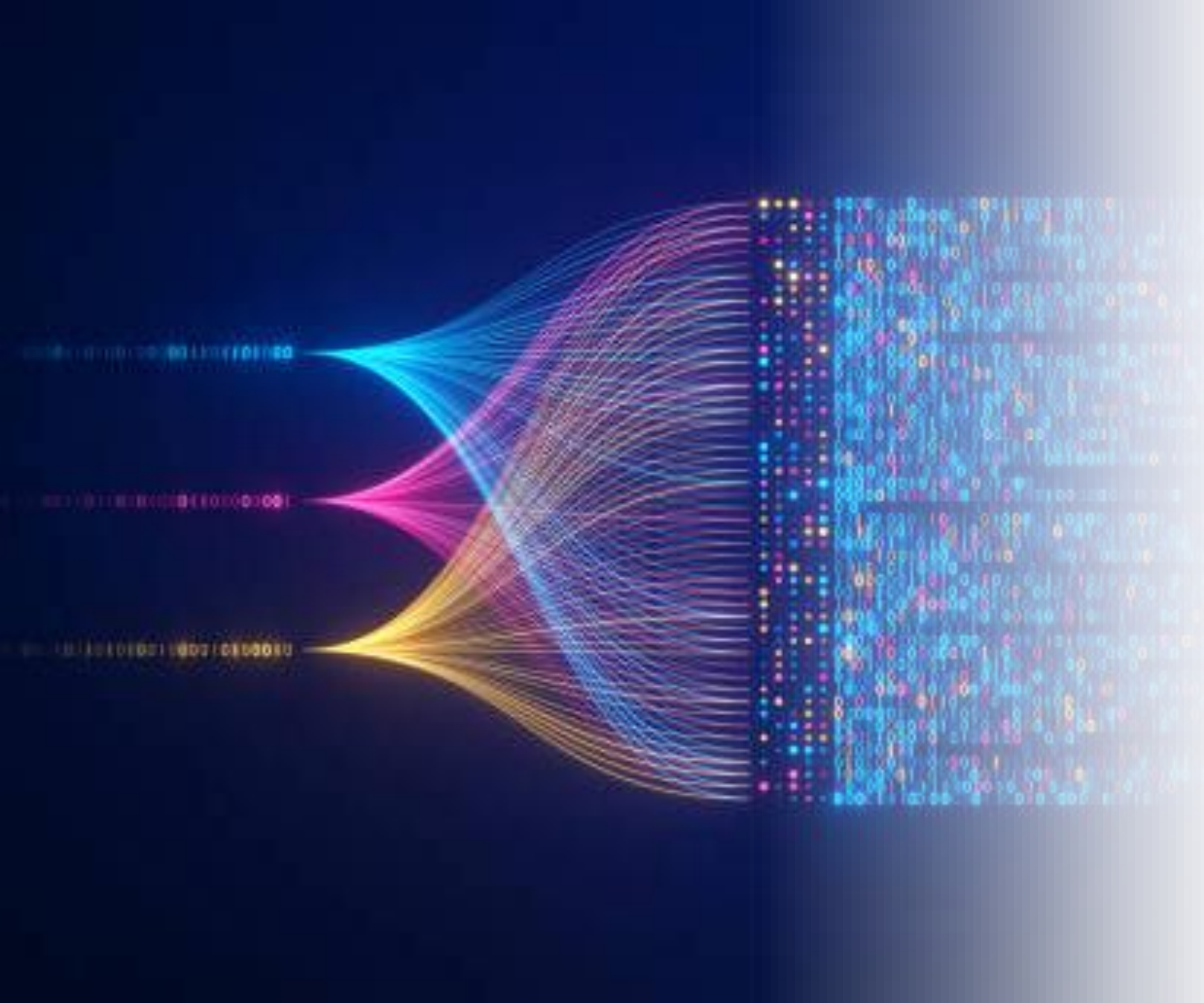
- **Does it make sense?**

General Considerations

Oversite and Monitoring of Troubleshooting

How is failure data captured:

- What do subjects do when tools/apps/devices fail
- When/how is the Clinical Investigator made aware of issues
- Back up plans for data collection
- When/how is the sponsor made aware of issues
- Plan if malware detected

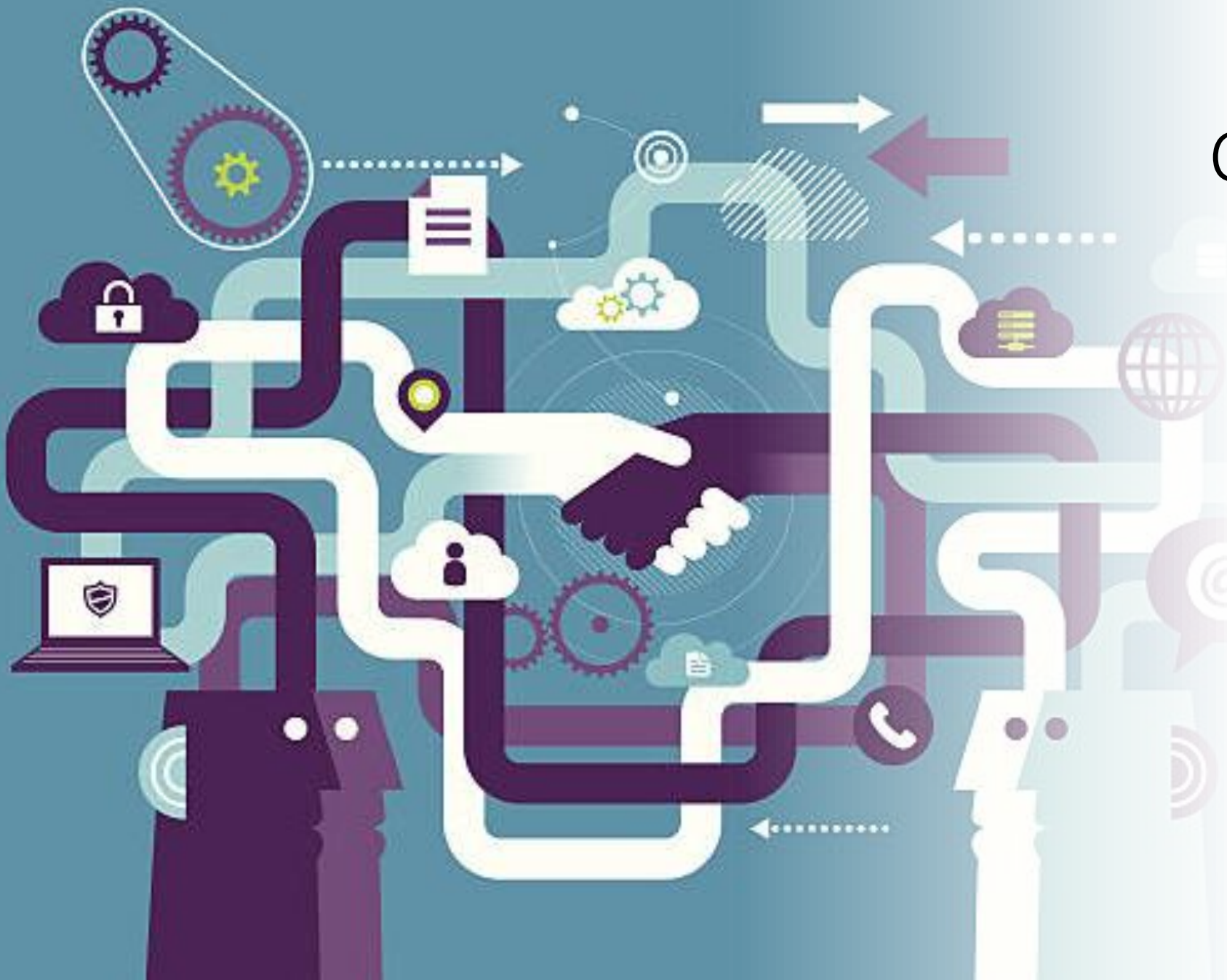


How is data transferred

- Complete?
- Accurate?
- Accessible?
  - Clinical site
  - Sponsor
  - Monitor
  - FDA Inspections

Consider how is data reviewed/accessed

- By the
  - Clinical Investigator
  - Monitor
  - Sponsor
  - FDA During inspections
- When is data available
- What accompanying data is maintained
  - Transmission data
  - Audit trail



Consider

When data is accessed by different parties:

- Does the view used allow access to the audit trail/or changes made
- When do sites/sponsors/monitors have access to data
- How will data be accessed after study closure

Oversight

- By the Clinical Investigator
  - How SAEs are reported
- By the Sponsor
- By FDA

Risk-based monitoring:

- Prioritize site based on site performance
  - Frequency and severity of protocol deviations
  - Number of participants
  - Clinical Investigator experience
  - Site staff experience
  - Historical site performance
  - Inspection findings
- Focus on critical data
- Use centrally available data from decentralized tools

Expectations during an FDA Inspection of a Clinical Investigator

- Regulations are followed
- Clinical Investigator has oversite
- Data collected for subjects at the Clinical Sites is available:
  - Health Records
  - Home Visit Data
  - Laboratory Results
  - Diary Data
  - Data from wearables
  - Shipping records for Investigational Product

Guidance

- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, 12/2023
- DRAFT GUIDANCE: Decentralized Clinical Trials for Drugs, Biological Products, and Devices, 5/1/2023
- Use of Electronic Records and Signatures***Part 11***Questions and Answers, 6/21/2017
- Use of Electronic Health Record Data in Clinical Investigations, 7/19/2018
- Use of Electronic Informed Consent, Questions and Answers, 12/15/2016
- Electronic Source Data in Clinical Investigations, 9/18/2013

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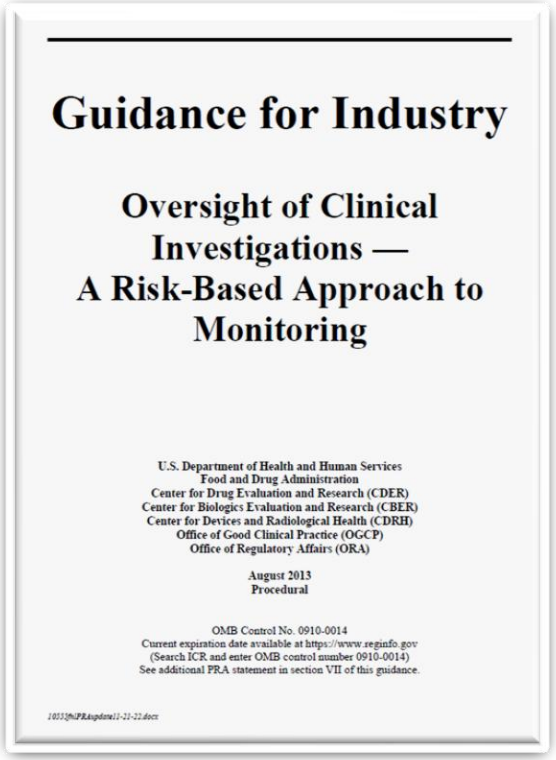
Guidance: Remote Monitoring



Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)

August 2013
Procedural

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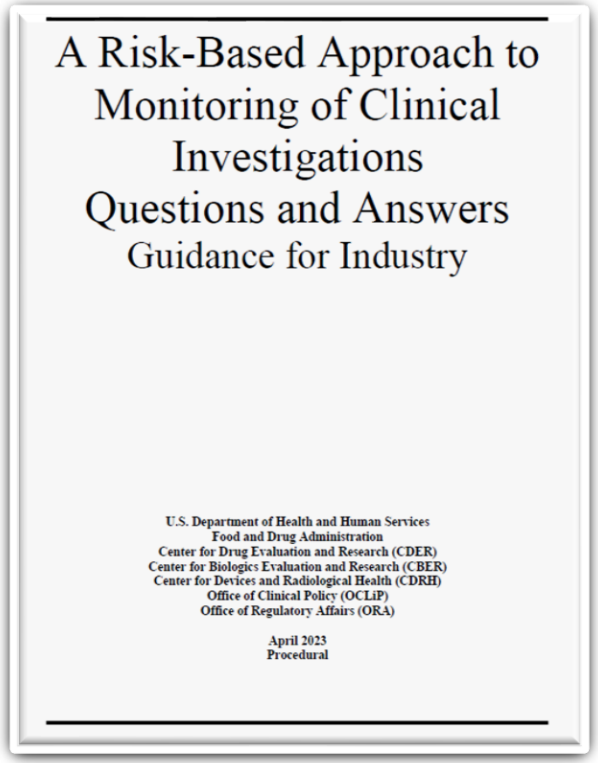
(Search ICR and enter OMB control number 0910-0014)
See additional PRA statement in section VII of this guidance.



A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Devices and Radiological Health (CDRH)
Office of Clinical Policy (OCLiP)
Office of Regulatory Affairs (ORA)

April 2023
Procedural

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Questions