Virtual Vigilance: Monitoring of Decentralized Clinical Trials

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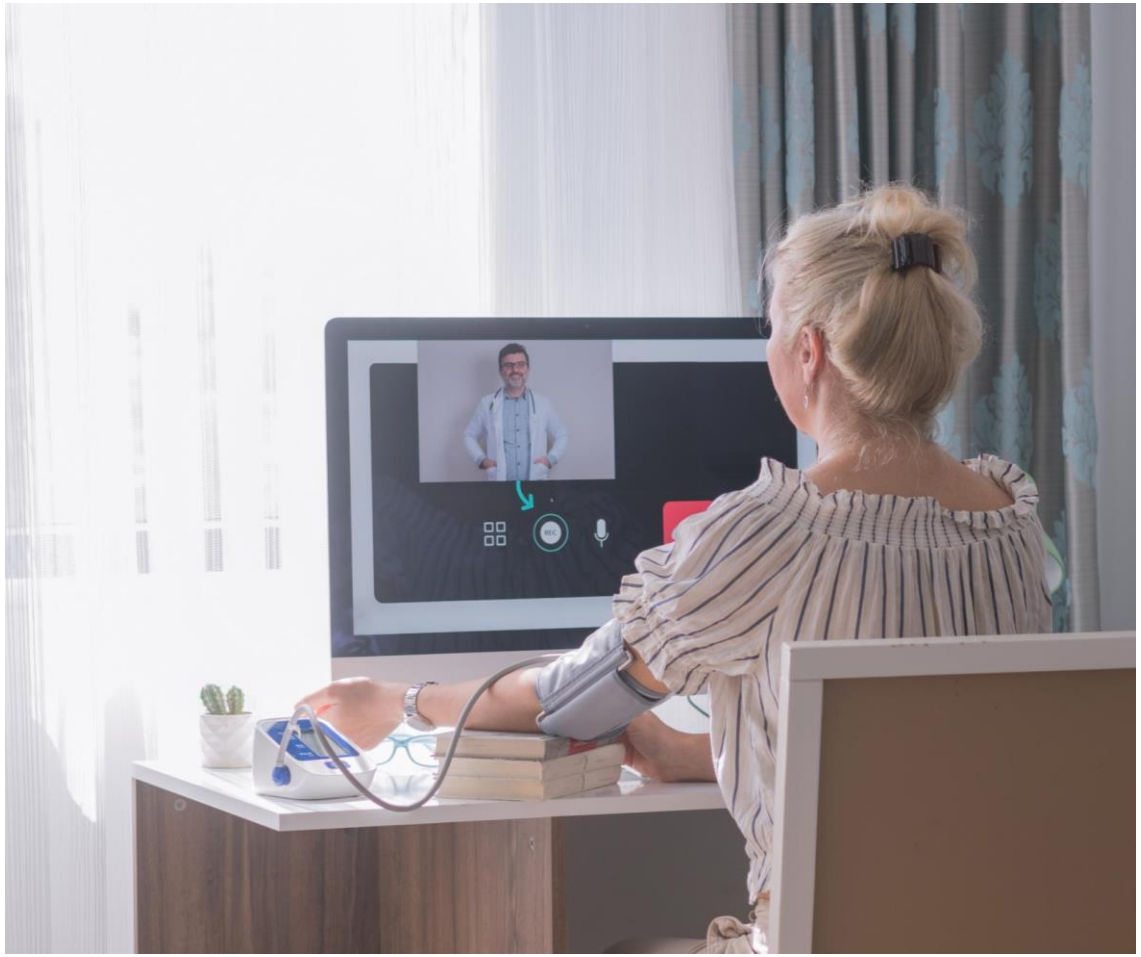
Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Topics: Virtual Vigilance of Decentralized Clinical Trials

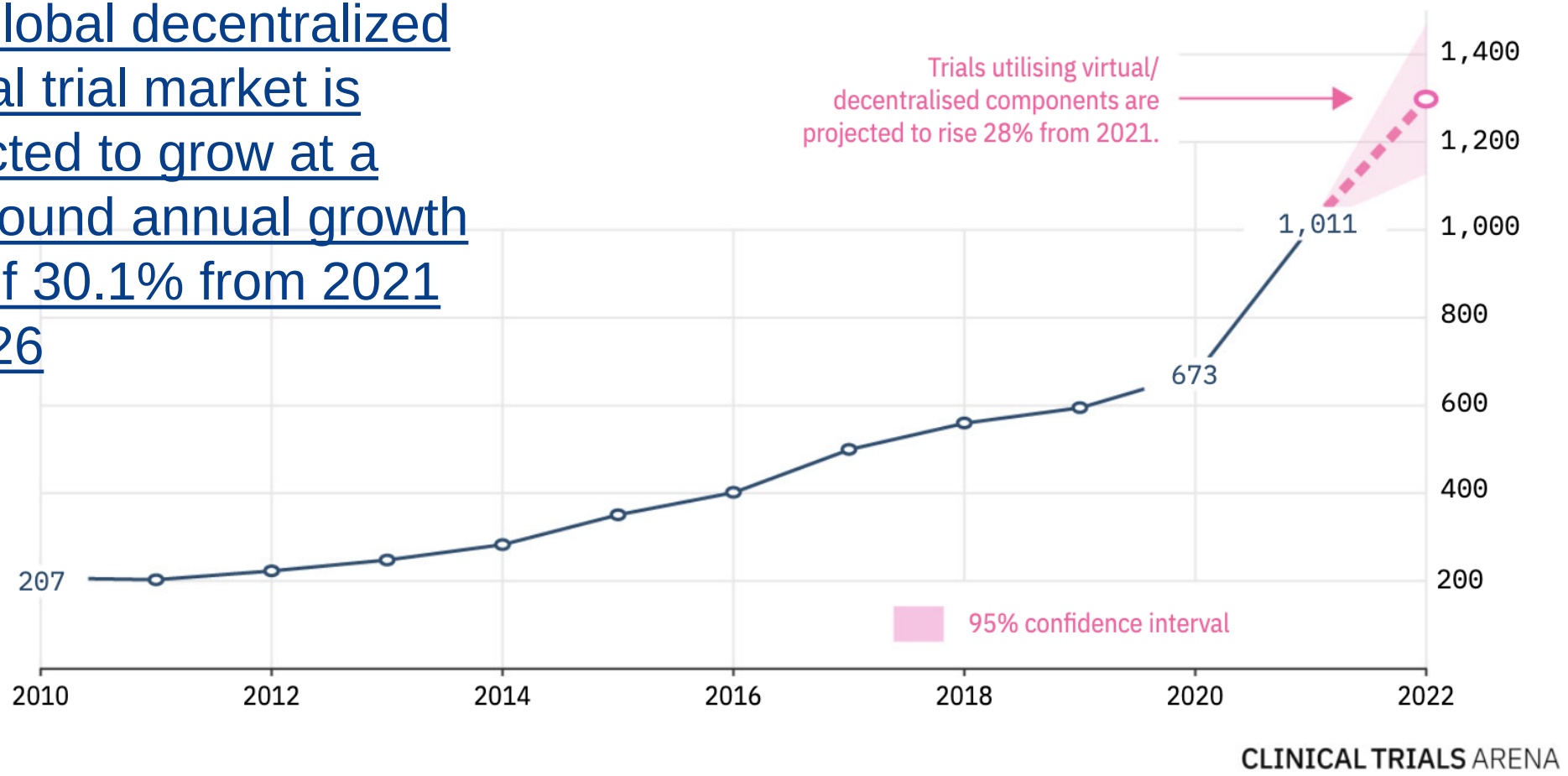
- What do we agree on?
- What are the guiding principles?
- What's the current approach?
- How do guidance(s) guide the way?
- How do we translate principles into "Virtual Vigilance"?



Images throughout created with Microsoft Co-Pilot or Adobe FireFly

Growing Need for Virtual Vigilance

The global decentralized clinical trial market is expected to grow at a compound annual growth rate of 30.1% from 2021 to 2026



https://www.researchandmarkets.com/reports

Growing Interest to Accelerate the Adoption of DCTs

DTRA
DECENTRALIZED TRIALS & RESEARCH ALLIANCE

Our Organizational Members

Advanced Clinical · AMGEN · astellas · Boehringer Ingelheim · buzzreach · CardieX · Care Access · careevolution · castor · CITELINE
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WORLDWIDE CLINICAL TRIALS · xCures · ZS

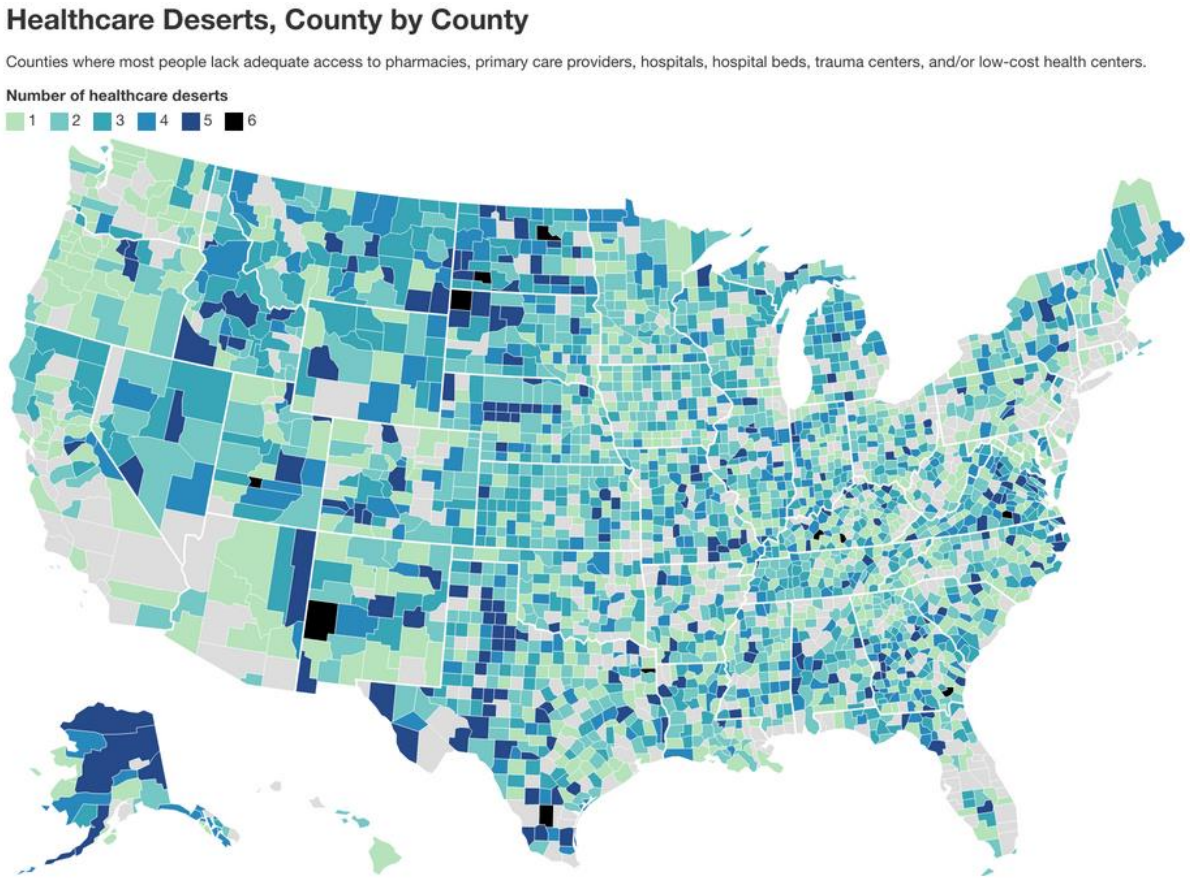
But a Few Concerns….

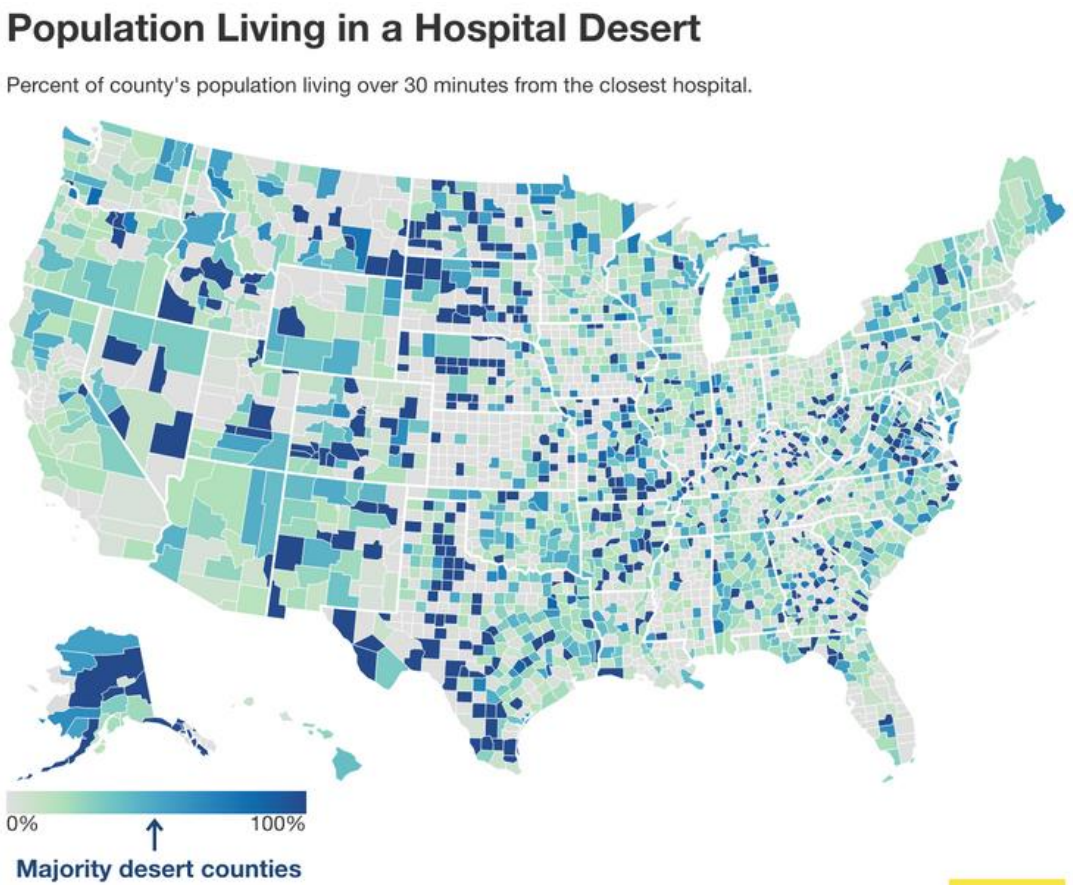
- Lack of standardization and validation
- Regulatory and ethical uncertainties
- Engagement vs. coercion
- Data security and privacy issues
- Technological literacy and access
- Resistance to change and adoption
- Lack of “safe” sharing

Raging Agreement

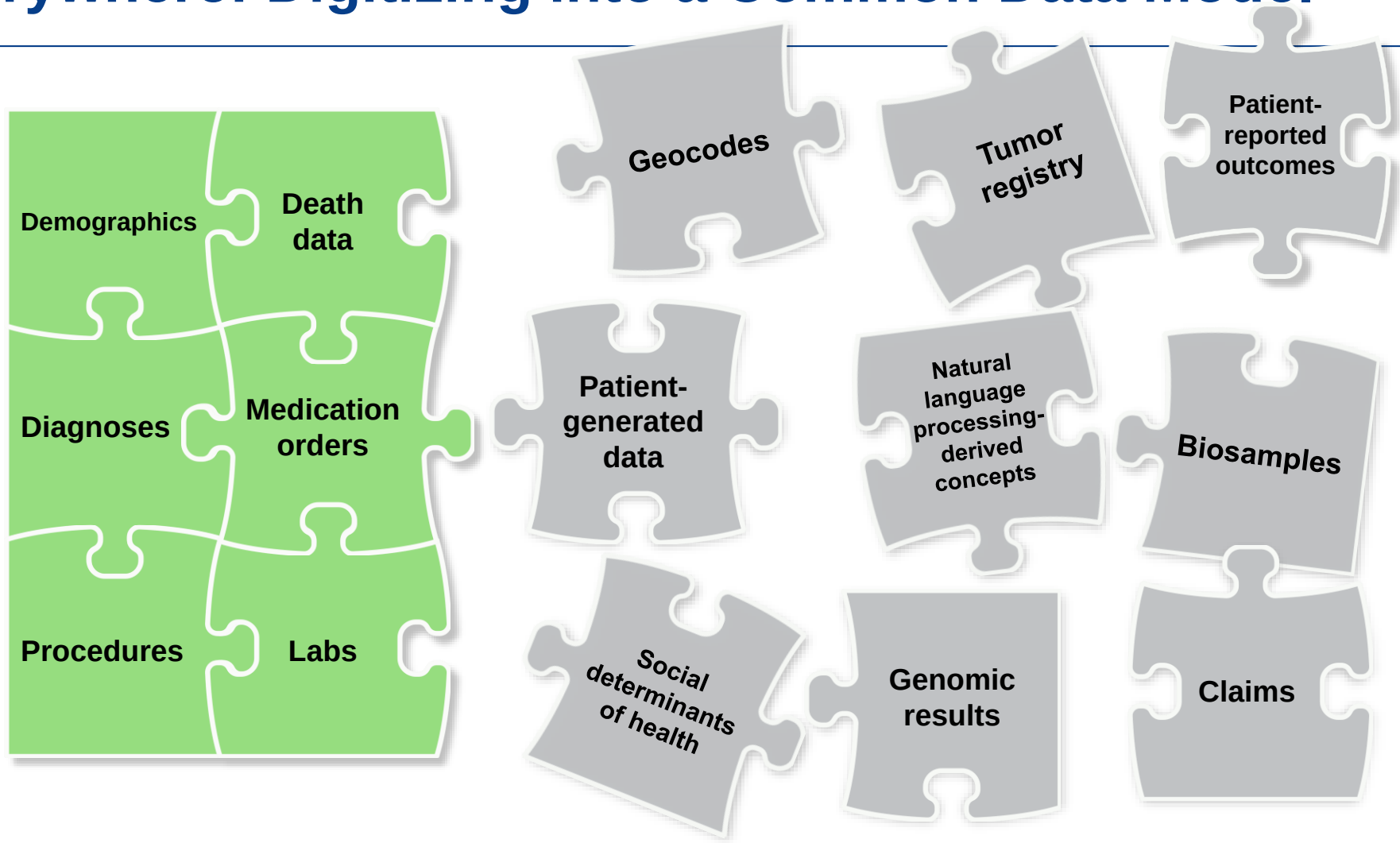
Trials need to meet the people!

Covering Clinical Trial Deserts





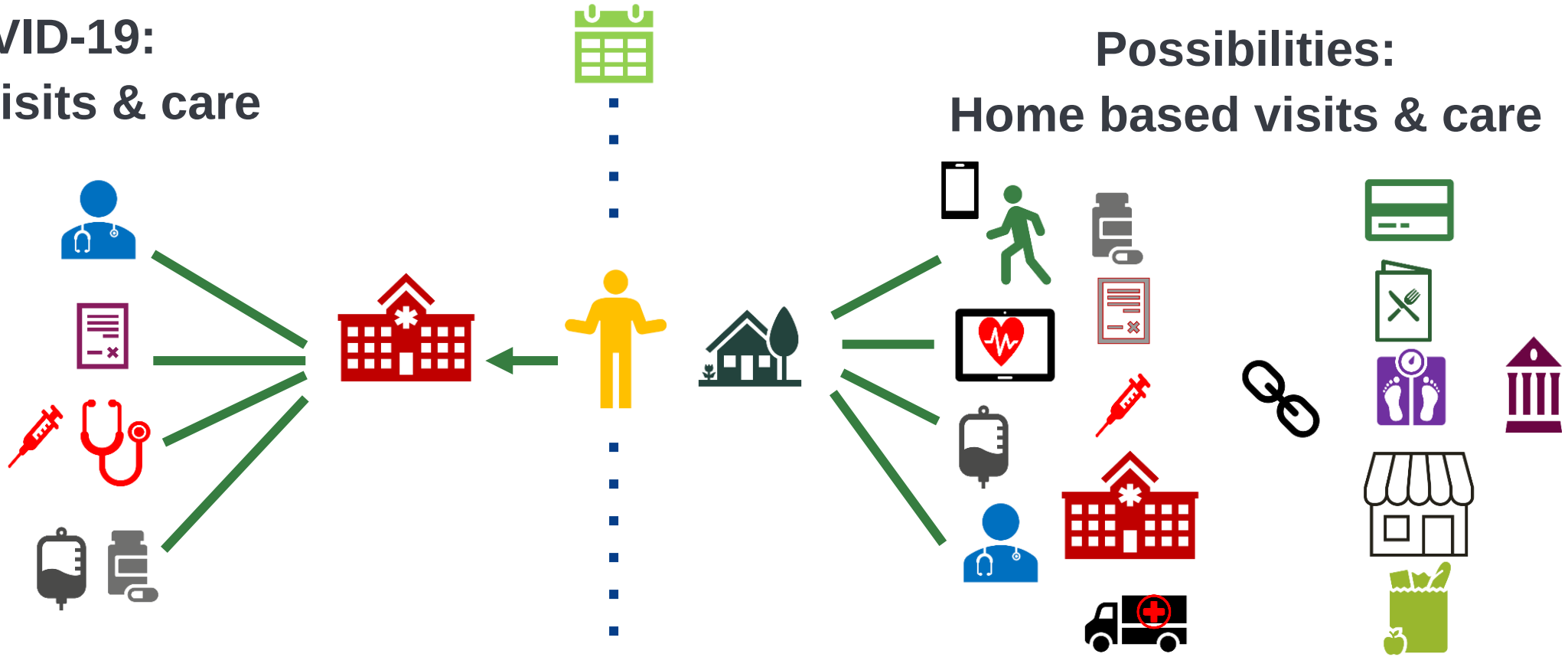
Data Everywhere: Digitizing into a Common Data Model



A Changed World of Possibilities: Pre-Covid to Post COVID

Pre-COVID-19:
Site based visits & care

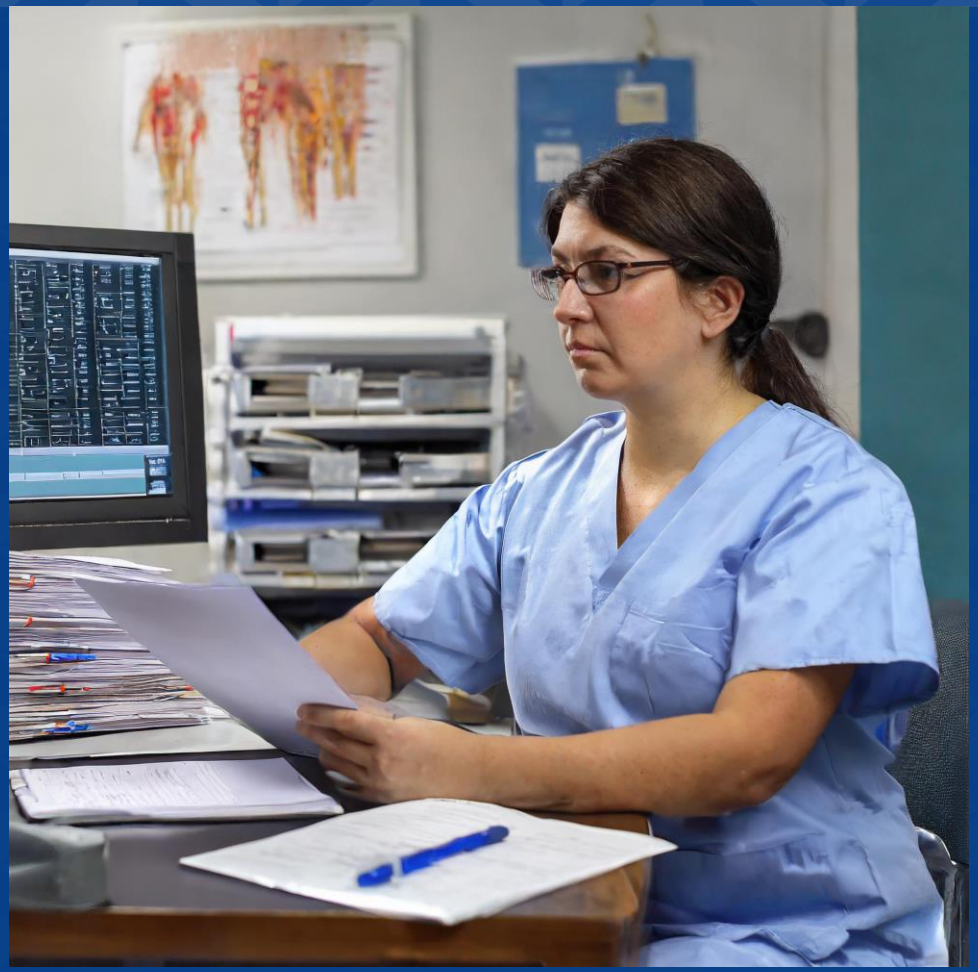
Possibilities:
Home based visits & care



CTTI

https://ctti-clinicaltrials.org/our-work/digital-health-

Guiding Principles & Current Monitoring Approach



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Guiding Principles — Defining Quality

- Have we enrolled the right participants according to the protocol with adequate **consent**? (*The Right Patient*)
- Did participants receive the **assigned treatment** and did they stay on the treatment? (*The Right Treatment*)
- Was there complete ascertainment of **primary and secondary efficacy data**? (*The Right Data*)
- Was there complete ascertainment of **primary and secondary safety data**? (*The Right Data*)
- Were there any ***major*** GCP-related issues? (*Do the Right Thing!*)

Califf, RM. Unpublished. Circa 1995

Traditional vs. Risk Based Monitoring

- Traditional Monitoring typically involves routine and **extensive** on-site visits to perform **source data verification for all data points**, regardless of their impact on the trial's overall risk profile
- Risk-Based Monitoring focuses on identifying and **managing potential risks** to critical trial data and processes that affect participant safety and **trial integrity**, allowing for more **flexible** and **targeted** monitoring efforts

Courtesy Dan Larson

Consider Translating Monitoring to a Digital World…

Contents

Courtesy Linda Lillis

Multi-Site Management Model

Monitoring CRA Team

- Primary contact for 35-50 sites
- Regular contact q 1-3 wks
- Feasibility & Reg Docs
- Training and Start-Up
- Delivering recruitment, retention and managing drug discontinuation
- Driving data currency and cleaning
- Follow up on Surveillance Reports & Action Items from on-site visit
- Remote drug accountability

Regional CRA Team

- On-site visits
- On-site ambassador and trainer
- SDV & consent review
- Study drug kits available & storage

Courtesy Dan Larson

DCRI 25 Years of Risk-Based Monitoring

Trial	Random % SDV	Risk-based	Initiation Visit	Visits/Year
1	15%		No	1–3
2	15%	50% rehosps	No	1
3	15%	100% hosp	No	1–2
4	20%	100% BL enzymes	No	3–4
5	15%		No	1
6	15%	25% BL, + hosp	No	2–3
7	20%	tSDV	No	2-3

Courtesy Dan Larson

Lessons Learned in RBM

- Regional differences in non-serious AE Reporting
- There are minimal discrepancies in SDV for routine outpatient visits
- Discrepancies with High Impact : $ Resource -- **High Value**
  - Inpatient hospitalizations
- Discrepancies with Low Impact : $$$ Resource– **Low Value**
    - Conmeds
    - Non-Serious AE's
- Typically ~20% of visits undergo SDV throughout the study
  - Including first 1-2 randomized
  - Higher proportion selected where hospitalizations occur (Impact)
  - Rare increase in SDV % based on risk indicators

Courtesy Dan Larson

Turning to Decentralized Trials: Lessons learned from DCTs

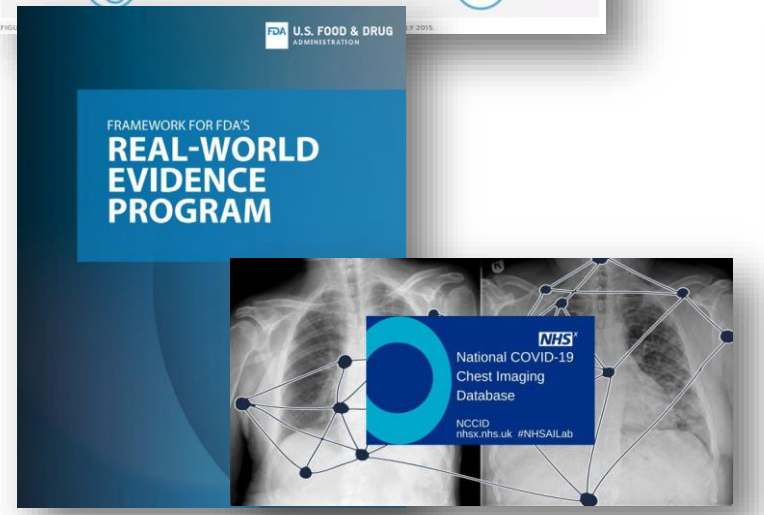
- The role of sites in managing patients is fundamentally different
- Establishing participant identity and eligibility remotely is not straightforward
- Tracking investigational product delivery and use can be challenging
- There are limits in what can be done to verify and clean participant reported data

We need to rethink monitoring to ensure the right patient, right intervention, right data, and right thing

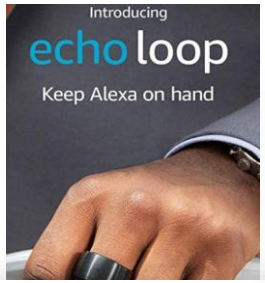
How does the Guidance Guide the Way?

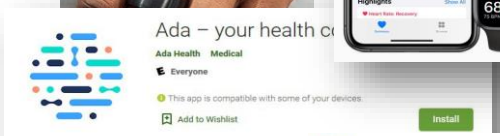
Lots of Regulatory Activities and Interest

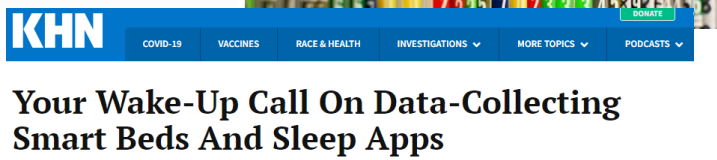
Advancing Evidence Generation Paradigm*



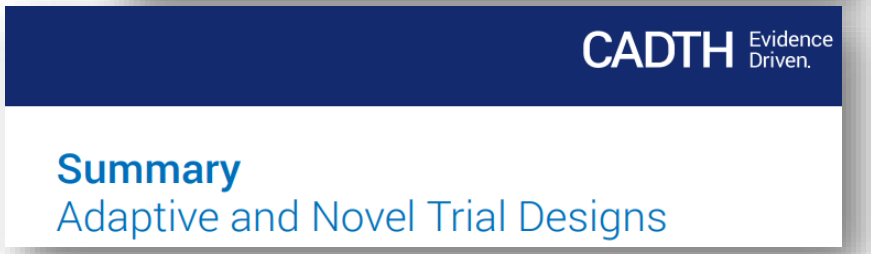
Increasingly Digital World & Data Availability*





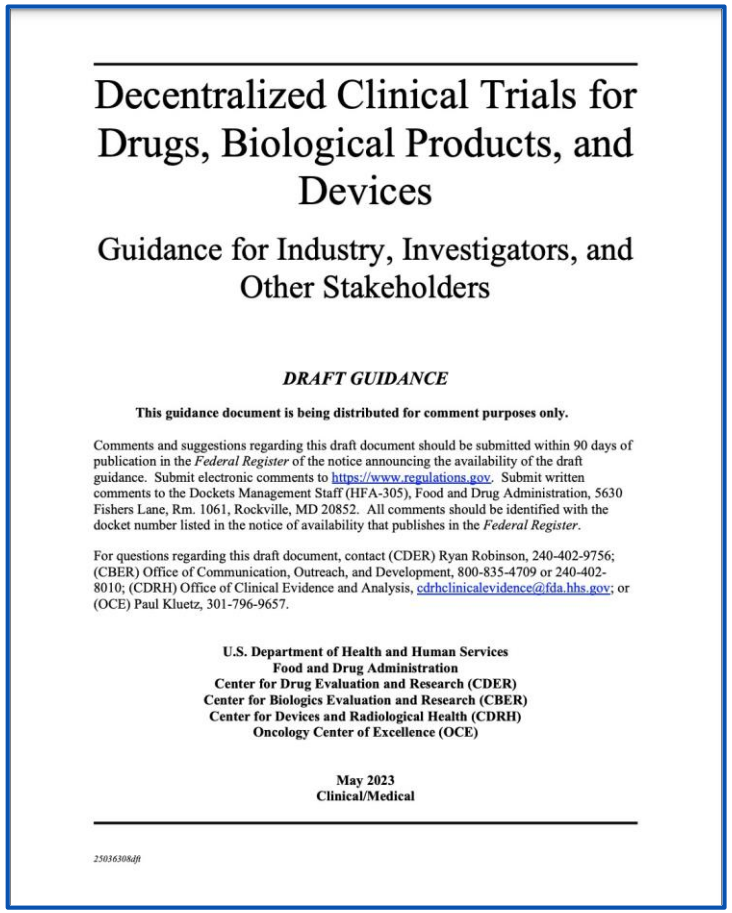


Innovative Clinical Trial Designs*



Adapted NIH Collaboratory Grand Rounds Harmonizing Good Clinical Practice Guidelines Aug, 2023

FDA Guidance- May 2023



Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ryan Robinson, 240-402-9756; (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, cdrhclinicalevidence@fda.hhs.gov; or (OCE) Paul Kluetz, 301-796-9657.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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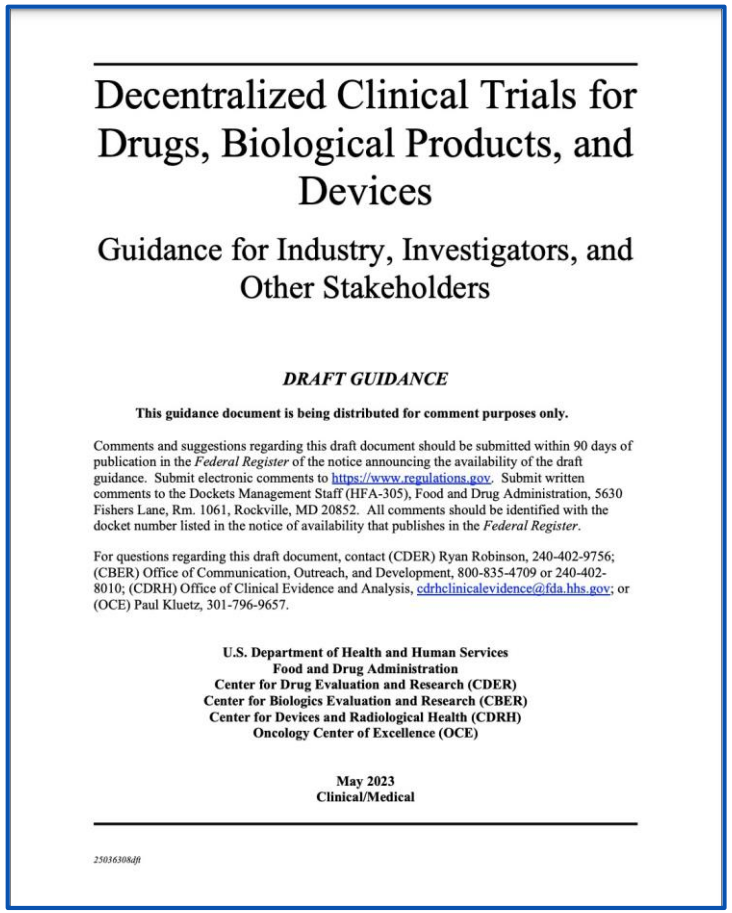
Oncology Center of Excellence (OCE)

May 2023
Clinical/Medical

25036308dft

https://www.fda.gov

FDA Guidance (May 2023)



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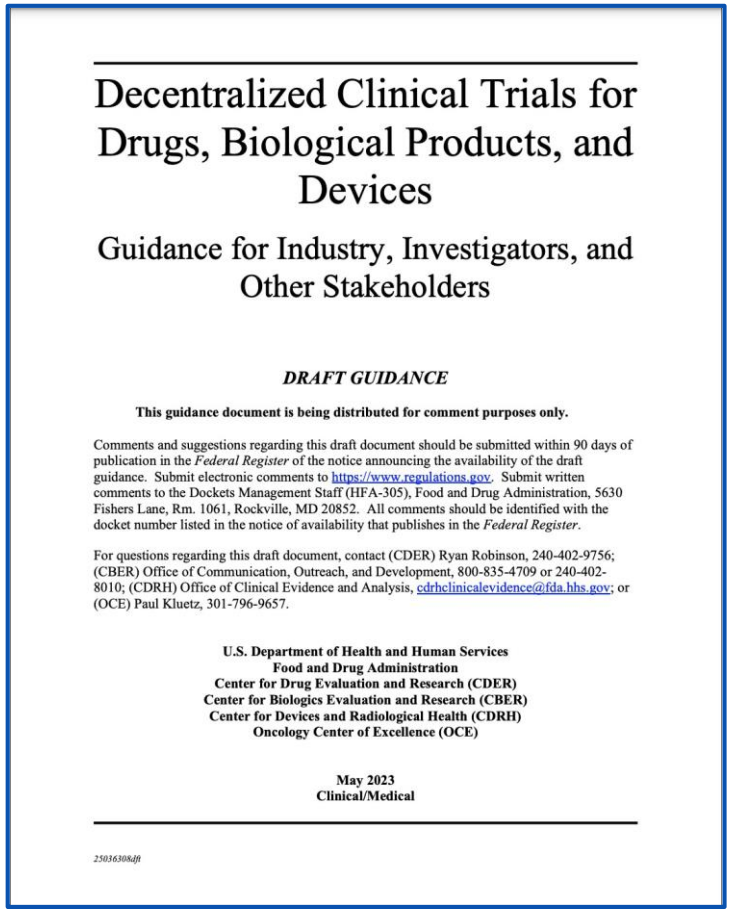
May 2023
Clinical/Medical

25036308dft

- Use **risk-based monitoring** methods and **centralized monitoring** to proactively identify and address missing data, inconsistent data, data outliers, and potential protocol deviations.
- Implement **quality by design** principles to ensure that the trial design, conduct, and analysis are aligned with the trial objectives and minimize risks to data quality and participant safety.
- Establish clear **roles and responsibilities** of the sponsor, investigators, and other parties involved in the DCT, and document them in a written agreement.

FDA Guidance



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- Ensure that the **informed consent** process is adequate, appropriate, and compliant with the applicable regulations and ethical standards, and that it incorporates the use of DHTs and remote visits in the DCT.
- Evaluate the **suitability** of the investigational products for use in a DCT, considering factors such as stability, storage, handling, labeling, and accountability.
- Develop a **safety monitoring plan** that specifies how adverse events, serious adverse events, and other safety information will be collected, reported, and managed in a DCT.
- Validate and verify the **software** used to support the conduct of a DCT, and ensure that it meets the requirements for data integrity, security, privacy, and reliability.

EMA Guidance (Dec 2022) & Differences

HMA Heads of Medicines Agencies

European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Version 01, 13 December 2022

Draft agreed by DCT project team (experts from Clinical Trial Coordination Group, Clinical Trial Expert Group, EMA scientific committees, EMA working parties, and EMA staff)	December 2022
Draft agreed Clinical Trial Coordination Group	December 2022
Draft agreed by Clinical Trials Expert Group	December 2022
Draft agreed by GCP Inspector Working Group	December 2022
Adopted by ACT EU Steering Group	December 2022

For questions related to this document, please write to secretariat of CTCG: ctcg@hma.eu

- Limited discussion of the health care provider
- Emphasis on importance of patient voice and input in an “early and sustained manner” as well as including investigators and providers in design, development and implementation.
- ⑩ Burden of DCT- related procedures must be weighted against the benefits for participants and PIs.
- Use of additional service providers in DCTs bring additional considerations to ensure proper safety procedures.
- Financial arrangement between the funder, investigator and service providers (including economic interests) should be detailed in the application to regulators.
- Differences that may affect data reliability should be discussed, including differences in the study population as well as differences in how measurement data is captured

EMA Guidance (Dec 2022) & Differences

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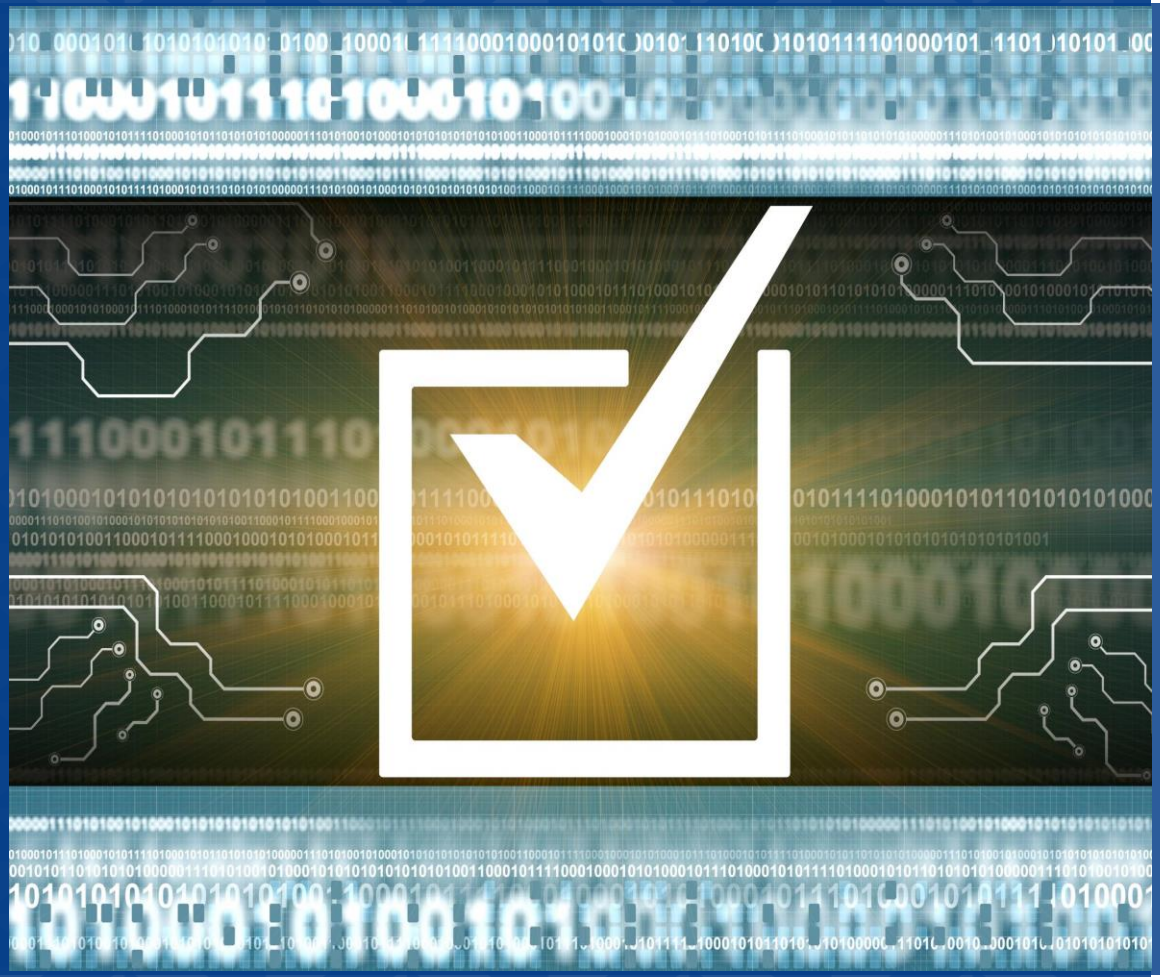
- Strategies for PI to support safety review of high-volume/sensor-derived data.
- Opportunity for an in-person visit if desired preferred; insurance should be in-place for any damage due to a trial-related procedure in the home.
- Delineation of Investigator vs Sponsor responsibilities/ well-defined and supported:
  - Considerations for many different stakeholders (service providers for home health or for technology)
  - Considerations for alternative processes for monitoring participant health and data
  - Sponsor must ensure qualification and experience for trial tasks but PI is responsible for their own due diligence and arrangement

Translating Principles into Virtual Vigilance



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FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

The Right Patient

- Monitoring inclusion and exclusion is routine

- Verifying identity is not common in RBM
  - Duplicate enrollment
  - Falsified or fabricated eligibility source documents
  - Data completion by surrogates

- Consider secure digital identification, two-factor authentication, or virtual/video visits
  - Where user credentialing and login is a barrier, consider technological solutions

The Right Intervention

- Getting study drug and other study materials into the hands of a participant requires distribution via mail or courier, breaking the traditional chain of custody. Issues include

  - Study medication going missing or being delayed *en route*
  - Refusal by mail/courier to deliver to participant's address
  - Mail/courier's reliance on PO Boxes or drop boxes for package pickup
  - Refusal of participant to accept study medication
  - Study medication returned by participant after receipt

- Under RBM, the process by which study materials get to participants should be considered high risk and monitored accordingly

The Right Study Procedures

- As roles for sites change, it remains critical that participants can be actively managed and that data about patient status can be acted upon, including mechanisms for
  - participants to ask questions and get timely responses
  - participants to report worrisome events
  - participants to report healthcare encounters or other events
  - tracking adherence to study intervention
  - tracking adherence to data collection procedures
- Solutions include a bi-directional EDC, MyChart for research, and active notifications to study personnel based on entered data

The Right Data

- Baseline state, treatment, outcome, and safety data are critical to understanding treatment benefits and risks
  - Baseline state and treatment are monitored as ‘right people and right intervention’

- Outcomes include patient reported outcomes, functional assessments including via digital technology, healthcare events, or mortality
  - All data submissions may require identity verification
  - Supporting documentation may include recordings of functional assessments, EHR data, or other information that can be uploaded for remote review
  - Note that release of medical records may be needed for health systems unrelated to the sites

New Issues to Consider

- Geographic distribution of participants
- Enrollment of two or more participants who share the same digital resource
- Enrollment of participants who do not have sufficient digital resources
- Rogue digital and social media recruitment practices

Summary of Primary Challenges for Monitoring DCTS

- Identity verification
- Chain of custody of investigational product
- Real-time participant management and communication
  - Adherence
  - Outcomes ascertainment
  - Event monitoring
- Navigating site role for participant management

Does AI Offer Solutions?

…or introduce a new set of monitoring challenges

EDITORIAL

AI IN MEDICINE

The Future of Clinical Trials

Artificial to Augmented to Applied Intelligence

Adrian F. Hernandez, MD, MHS; Christopher J. Lindsell, PhD

Table. Opportunities and Risks for Artificial Intelligence (AI) in Clinical Trials

	Opportunities	Risks
Engagement and recruitment	Multifaceted engagement with potential participants likely to contribute informative data	Bias in who is approached, coercion, and where a trial is deployed
Consent	Bidirectional, ongoing, informed consent process tailored to the participant in terms of delivery, language, cultural context, and understanding	Inadequate informed consent, coercion, misunderstanding of benefits vs risks
Participant management	Customized study procedures, ongoing engagement with complete follow-up	Bias in adherence to study procedures and loss to follow-up, failure to identify safety issues
Data capture and curation	Comprehensive data set describing all health domains of interest for every participant	Incomplete data, inaccurate data, inaccurate linkage among data sources, misappropriation or misuse of data
Outcomes and safety ascertainment	Completely captured clinical and patient-reported outcome trajectories	Missing outcomes, misattribution of outcomes
Data analysis and reporting	Automated reporting integrated with interpretation based on all information available globally	Inappropriate data manipulations, improper causal inference
Dissemination and implementation	Trial results reported to participants, communities, and clinical communities	Inequitable dissemination and lack of implementation

Hernandez AF, Lindsell CJ. JAMA. 2023 Nov 11

Conclusions

- **Virtual Vigilance:**
  - Needed for the growing market of decentralized clinical trials
- **Decentralization of Trials Present Interesting Challenges:**
  - General: standardization, data security, and technological literacy
  - Study Specific: identity verification, chain of custody, and real-time participant management
- **Apply Quality By Design & Risk-Based Monitoring:**
  - Focus on identifying and managing potential risks to critical trial data and processes
- **Be Smart:**
  - Consider new methods offered by virtual vigilance
- **Stick to Guiding Principles:**
  - Ensuring the right patient, right treatment, right data, and doing the right thing