




Decentralized Clinical Trials: Design, Method & Data Considerations

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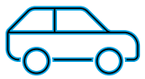
OUTLINE

- Background
- Study design
- Method
- Data
- Concluding remarks

WE NEED TO MAKE CLINICAL RESEARCH ACCESSIBLE AND CONVENIENT

WE KNOW THAT:

Fewer than 5% of eligible patients participate in clinical trials.[1]



Barriers to participation, including time off work, time to travel to sites, and other inconveniences can be a significant deterrent.[2]

Across a number of disease areas, racial minorities are at increased risk yet are under-represented in clinical trials.[3]

DECENTRALIZED CLINICAL TRIALS CAN HELP US:

- Increase access to potential patients [4]
- Remove barriers for trial participants [5]
- Enhance diversity in trial participants [5]

[1] 2020 Clinical Trials in the Age of Coronavirus | Medidata Solutions - Medidata Solutions
[2] 2019 Assessing Patient Participation Burden Based on Protocol Design Characteristics - PubMed (nih.gov)
[3] 2018 Addressing Diversity in Clinical Trials - PharmaVOICE : PharmaVOICE

[4] 2019 Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations - PubMed (nih.gov)
[5] 2018 Decentralized Clinical Trials | Clinical Trials Transformation Initiative (ctti-clinicaltrials.org)

CONVENIENCE TO PARTICIPANTS

Burden of clinical trial participation is compounded by the:

- Number and frequency of study procedures
- Invasiveness of study procedures
- Disruption to routine
  (e.g., time off work, unfamiliar procedures)
- Time dedicated to study activities
  (e.g., length of study visits, travel, parking)

Decentralization will **help reduce both time and disruption to routine** for trial participants

Further, by implementing Value Based Research (applying essentialism to design) along with designing studies with decentralization in mind, we will also **reduce the number and frequency of study procedures**

Participating in a clinical trial should add as little burden as possible to what a patient already experiences.

FROM SITE-CENTERED TO DECENTRALIZED

Pre-COVID: Site-Centric Paradigm

Site Staff

Sites largely identify patients through their databases

Protocol visits solely at investigator site

Site Staff

Paper, in-person Consent

Patient driving to site every visit

Most assessments conducted at stie

Data collection at site

Future State: Decentralized Paradigm

Enrollment

Add and enhance recruitment capabilities

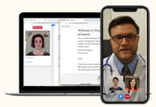
Digital Recruitment

Recruitment Partnership

Patient

Visit Activities

Transform delivery so that many protocol procedures are designed to be conducted remotely



Telemedicine

Mobile Healthcare

Local service provider (e.g. Minute Clinic)

Local lab collection & Imaging

Full e-data capture (e.g., EMRs, wearables)

Local drug delivery & dosing

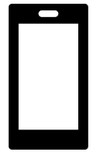
What is NOT changing:	▪ Investigators are responsible for oversight of trial participants and trial records ▪ Same high standards for patient safety, trial integrity, and data quality

DECENTRALIZED CLINICAL TRIALS

Clinical Trials which are executed through telemedicine and mobile/local healthcare providers, using procedures that vary from the traditional clinical trial model.

Clinical Trial Transformation Initiative

DIGITAL HEALTH*



mobile health

health IT

wearable devices

telehealth and telemedicine

personalized medicine

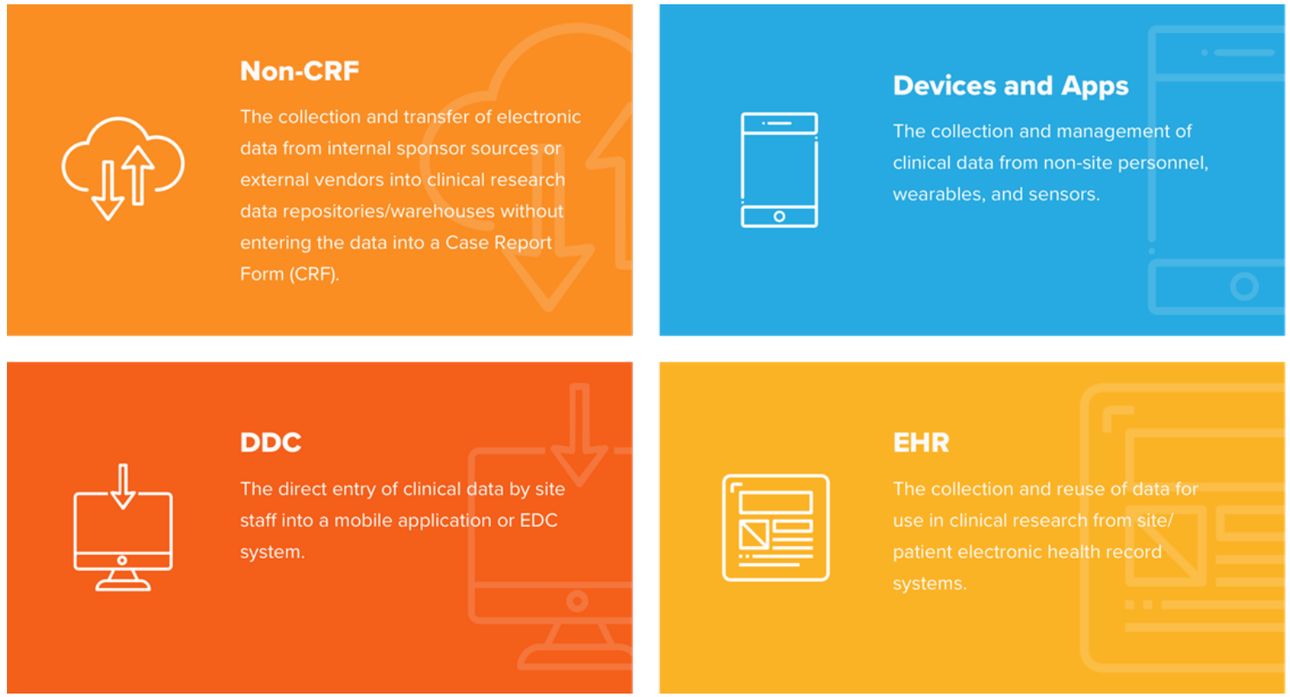
Advantages

- Holistic view of patient health
- Improve our ability to accurately diagnose and treat disease
- Enhance delivery of health care
- Reduce costs
- Make medicine more personalized for patients

* *Definitions from* Digital Health Center of Excellence | FDA

ELECTRONIC SOURCE DATA*

FDA defines this as data initially recorded in electronic format



Advantages

- Eliminate unnecessary duplication
- Reduce transcription error
- Facilitate remote monitoring and promote real-time access
- Facilitate accurate and complete data collection

* *Definitions and Value statement of eSource from* TransCelerate - Esource Clinical Trials Assets (transceleratebiopharmainc.com)

REGULATORY LANDSCAPE ON DCT

- "*…more trials can incorporate data from electronic health records, and adopt electronic informed consent, to enroll more patients in clinical trials closer to where they live and work...*" Scott Gottlieb (2019)*
- FDA in collaboration with Clinical Trial Transformation Initiative
- Danish Medicine Agency's guidance on the implementation of decentralized elements in CT with medicinal products
- Trials@Home+ sponsored by IMI aims to reshape CT design, conduct and operations

*Statement by FDA Commissioner Scott Gottlieb, M.D., on new strategies to modernize clinical trials to advance precision medicine, patient protections and more efficient product development | FDA

+Trials@Home | IMI Innovative Medicines Initiative (europa.eu)

DCT CHALLENGES

Limited regulatory guidances

Regional differences in DCT capabilities

Data security and quality concerns

Lack of data standardization

KEY STATISTICAL WORK

- **Design** clinical trials that will help more patients gain access and make participation more convenient
  - Essentialism
  - Endpoint validation
- Create robust **method** and statistical analyses plan
  - Mixed modality
  - Multiple raters
  - Simulation work
- Plan for remote **data** collection and anticipate questions from regulatory
  - Generate evidence to support future remote assessments
  - Standardization of remote assessments

STUDY DESIGN CONSIDERATIONS

TRIAL DESIGN ELEMENTS

- Primary and secondary endpoints: in-clinic vs remote?
- If remote assessment
  - how to conduct and standardize assessments
  - what factors can impact assessments
- Country/regional considerations for remote data collection –> mixed modality?
- Opportunity to assess reliability of in-clinic vs remote data collection

CLINICAL OUTCOME ASSESSMENTS

COA is a measure that describes or reflects how a patient feels, functions, or survives.

Patient reported outcomes (PROs)	Clinician reported outcomes (ClinROs)	Observer reported outcomes (ObsROs)	Performance outcomes (PerfOs)
• Patients' health condition directly reported by the patients	• Patients' behavioral and event assessments reported by HCP	• Patients' behavioral and event assessments reported by caregivers	• Patients to complete a well-defined task

CLINICAL OUTCOME VALIDATION

- Need to understand the difference (bias and variability)
- Validation is important for ensuring that a test, tool, or instrument is adequate for its proposed use
  - Can be relied upon to provide a given interpretation in the specified context of use
  - Use of COA with insufficient sensitivity to detect change could result in CT that fail to detect a treatment effect when one exists
- Careful considerations for remote data collection of ClinRO and PerfO should be given

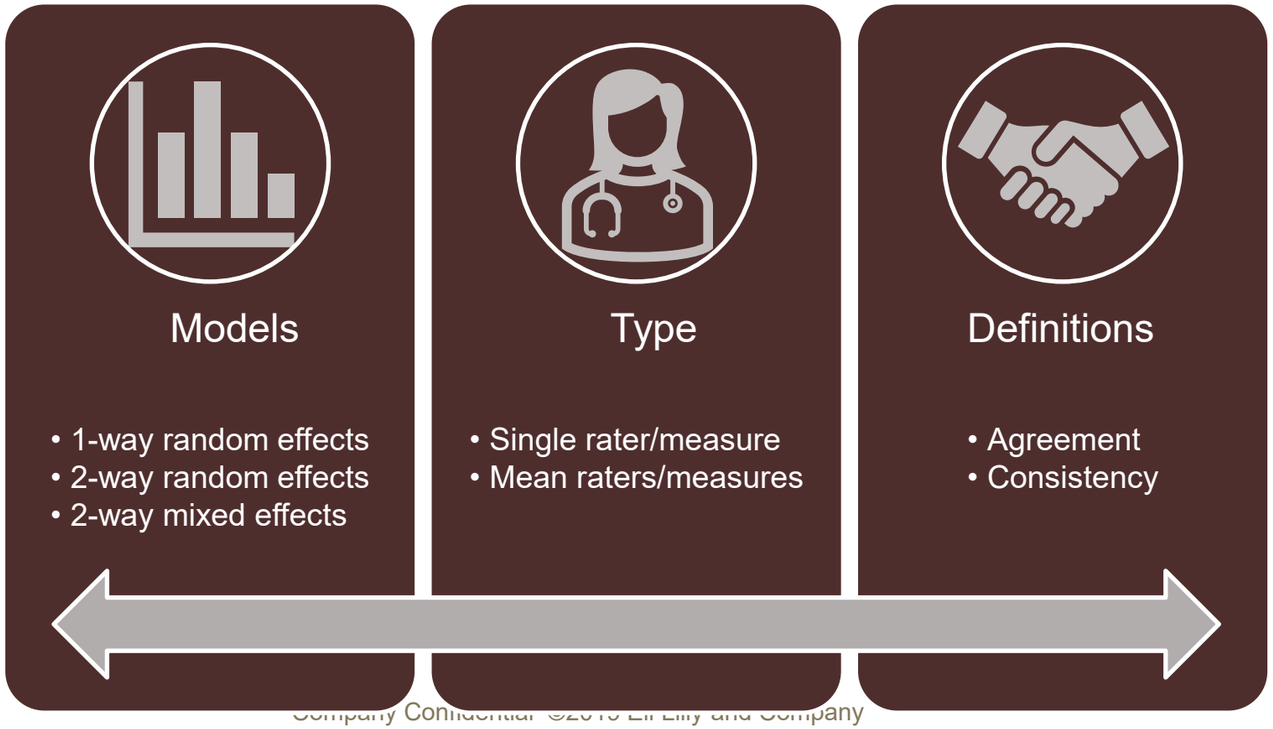
VALIDATION STUDY

- Stand alone or sub-study to evaluate the usability and comparability of in-clinic vs remote assessments
  - Cross-over design
  - Data can be used to generate evidence to support future use of remote assessments
- Sample size justification: hypothesis testing, estimation of intraclass correlation coefficient (ICC)

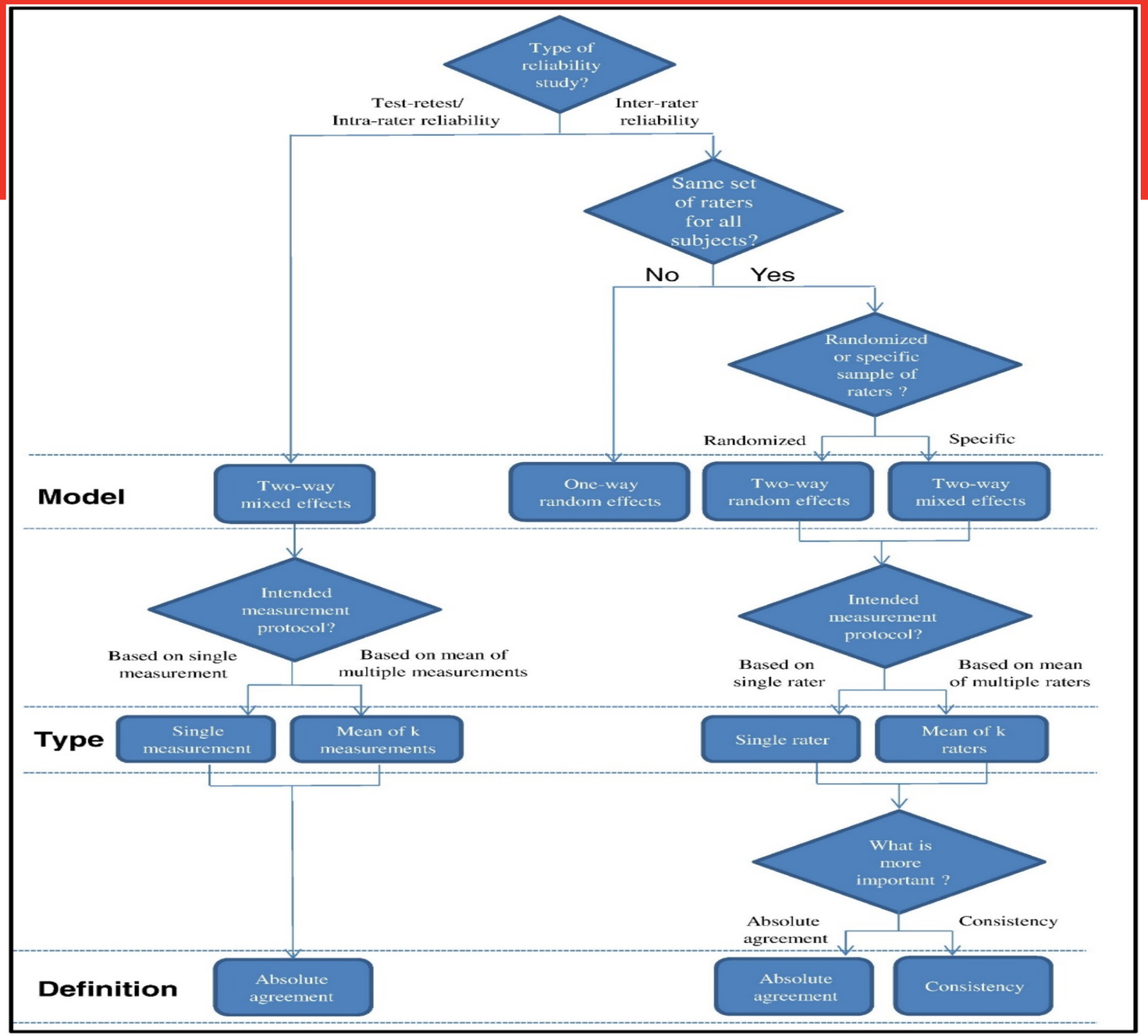
METHODS CONSIDERATIONS

INTRACLASS CORRELATION COEFFICIENT (ICC)

- ICC provides flexible framework of statistics for measuring reliability
- Reliability = true var/(true var + error var)
- ICC refers to correlations within a class of data (i.e., repeated measurements of weight), rather than correlations between different classes of data (i.e., correlation between height and weight)
- ICC has a Range in [0, 1]
- Different forms of ICC

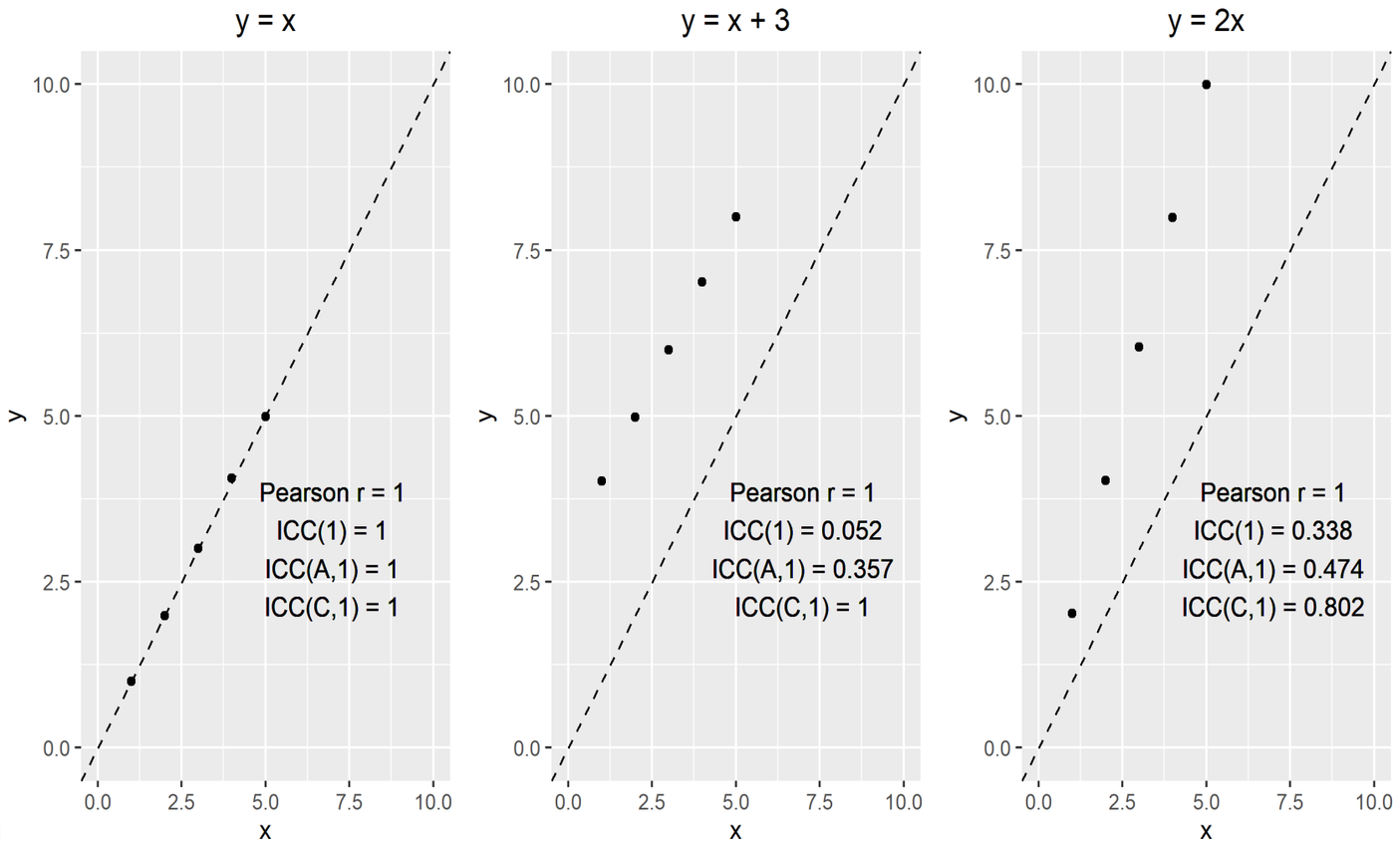


ICC FLOWCHART (KOO & LI, 2016)



ICC EXAMPLE

Single rater case shown with toy example (computed using psych::ICC in R)



Provided by Albert Man

REPORTING OF ICC

- ICC software is readily available
  - R package, ‘ICC’ function from ‘irr’ or ’psych’ package
  - SAS program, PROC MIXED, PROC GLM, PROC NLMIXED, %INTRACC macro
  - SPSS
- ICC should be reported along with
  - Model: 1-way or 2-way
  - Rater: single or multiple raters
  - Definition: consistency or absolute agreement
  - Confidence intervals
  - Characterization of reliability

Level of reliability/ Repeatability outcome	Estimated ICC	
	Koo & Li (2016)	Cicchetti & Sparrow (1981)
Poor	<0.50	<0.40
Moderate	0.50 – 0.75	0.40 – 0.60
Good	0.75 – 0.90	0.60 – 0.75
Excellent	0.90 – 1.00	0.75 – 1.00

ICC RECOMMENDATIONS

For assessing reliability of in-clinic vs. remote data collection

- Use 2-way mixed-effect, single-rater model with absolute agreement as a primary measure of agreement between in-clinic vs. remote assessment
  - Consistency ICC as exploratory measure to detect the presence of any bias between in-clinic and remote assessment
- For each subject, we recommend the same rater conducts both remote vs. in-clinic assessment to remove rater variability and only consider remote vs. in-clinic variability

MIXED MODALITY

- For a given patient, data is collected in-clinic and remotely:
  - Subject level random effect
  - Interaction between treatment and modality in the model
- Certain countries/regions have limited remote data collection capabilities:
  - Sensitivity analyses
- Opportunity to conduct simulation work to evaluate data with mixed modality on statistical inference

MISSING DATA

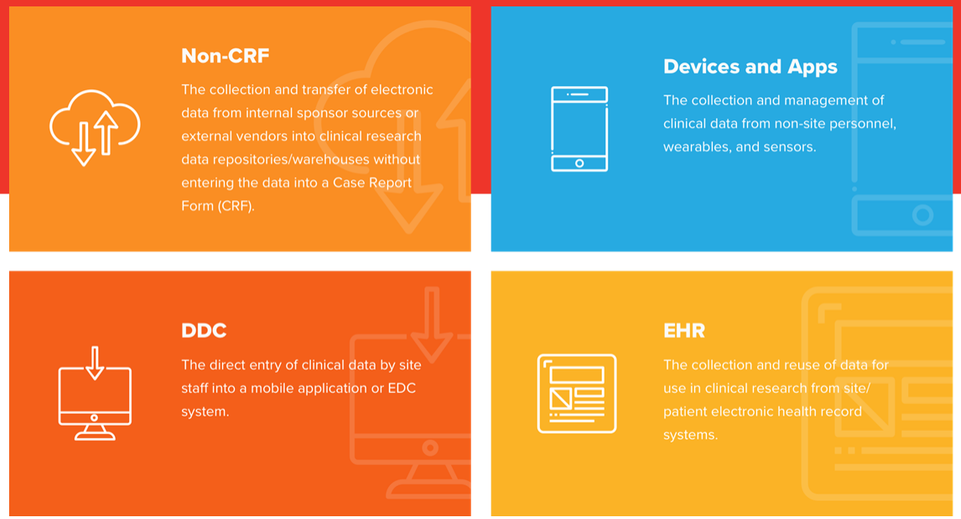
- Missing data in DCTs occur as they do in traditional CTs
  - Reasons could be specific to remote or digital data
  - Missing data mechanism may be different
- Capturing specific information at the participant level to describe the post-randomization events will be useful
- Study team should monitor data early to identify any potential patterns

DATA CONSIDERATIONS

GENERAL DATA PRINCIPLES

- ICH E9 guideline “Statistical principles for clinical trials” states that collections should focus on essential data to implement the planned analysis
  - Site and patient burden vs potential benefit of the analyses should be considered
- All data be reliable and accurate
  - Data integrity is defined as the extent to which all data are complete, consistent, accurate, trustworthy, and reliable throughout data lifecycle
  - ALCOA+ principles apply

eSOURCE DATA



- Statisticians and data strategists should always be included in critical data collection modality, operational, and implementation choices

- Intent is to improve site and participant experience by reducing data collection burden while providing near real time access to quality data for decision making

MINIMIZE MISSING DATA

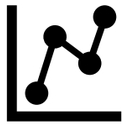
Device Design: Alerts can and should be built into the eSource system to either remind the user to answer questions or notify them of incomplete data

- Email alerts can also be set up to notify of missing critical data such that missing data might be completed within an appropriate recall period

Technical Support: When using eSource, 24/7 technical support from the vendor becomes critical to prevent data loss

- Back-up/replacement devices need to be readily available

Training: Robust training for all users of eSource collection devices and apps must be available and readily accessible for a review/refresher as needed



Start of Collection: Much consideration should be given to the start of device data collection such that enough data is collected to ensure a proper baseline measurement

DATA CORRECTIONS

Recall periods: It is difficult to query data collected via eSource

- This drives the need to ensure data is entered correctly the first time
- Design that minimizes entry error is critical
- Involvement of site personnel and patients in the design and usability of eSource solutions

Data query: after a reasonable recall period should be done with great caution

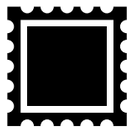
- In some cases, there may be other contextual data that provides support for the data correction
- Determine a consistent and timely approach to data corrections and ensure it aligns with regulatory

Auto query: More extensive use of auto-queries at the time of data capture may be possible especially for DDC

- For eCOA, one must consider whether the data collected are validated scales
- Any inclusion of auto-queries to guide correct completion must not affect the scale validation

Attributable: All data corrections must ultimately be either initiated or approved by the originator of the data and attribution of the data correction must be visible within an audit trail

DATA OVERSIGHT



Device date/time stamp calibration: Be mindful of how the date time stamp is set and calibrated for each device

- Understand device battery life and the effect of a low battery on device time settings

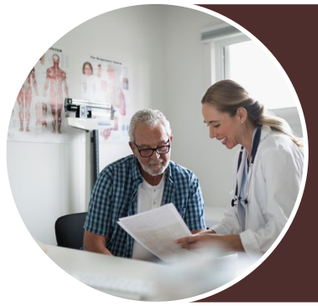
Data monitoring: Central monitoring of collected data and the associated meta data (audit trail data) should be done from the beginning of the trial

- This will allow the early identification of issues so that timely corrective actions are implemented, and preventive actions are planned

Compliance reports: Early oversight of compliance reports will identify site or participant trends in missing or erroneous data

- The earlier these issues are identified and corrected, less erroneous or missing data .

CONCLUDING REMARKS



DCT enables clinical trials more accessible and convenient, contributes to a healthy ecosystem of clinical trial research

DCT has challenges

- Limited regulatory guidances
- Regional differences
- Data security and quality
- Lack of standardization

Key statistical work: essential design elements

- Mixed modality
- Endpoint validation
- Multiple raters
- Data standardization, oversight, correction

BACK UP

ABSTRACT

The pandemic has changed the landscape of clinical trials to be more patient centric and to enable continuous access for patients to health care and promising medicines through the decentralized framework. Decentralized approach may include capabilities such as digital recruitment, telemedicine, mobile health care, and digital health tools (DHT). Decentralized Clinical Trial (DCT) can increase trial access by expanding geographic boundaries and patient demographic representations; thereby, increasing generalizability of the trial result and reduce bias. At the same time, DCT present challenges with lack of standardization of remote data collection and DHTs, potential mixed modalities of data collection and technical interruption which can lead to additional variability associated with the outcomes of interest and missed opportunity on identifying potentially effective treatments. In this talk, we will discuss study design, method, and data considerations in DCT to overcome these challenges and to generate the scientific evidence needed for promising investigative treatments.

INTRACLASS CORRELATION COEFFICIENT (ICC)

- Flexible framework of statistics for measuring of the reliability of two or more raters to measure subjects
- ICC refers to correlations within a class of data (i.e., repeated measurements of weight), rather than correlations between different classes of data (i.e., correlation between height and weight)
- ICC reflects both the degree of correlation and agreement (Range in [0, 1])
  - One-way model and population ICC (single-rater)
    - $x_{ij} = \mu + r_i + w_{ij}$
    - $\sigma_r^2/(\sigma_r^2 + \sigma_w^2)$
  - Two-way model and population ICC (single-rater)
    - $x_{ij} = \mu + r_i + c_j + e_{ij}$
    - Consistency: $\sigma_r^2/(\sigma_r^2 + \sigma_e^2)$
    - Absolute agreement: $\sigma_r^2/(\sigma_r^2 + \sigma_c^2 + \sigma_e^2)$

$i = 1, \ldots, N$ participants
$j = 1, \ldots, J$ raters
r_i = mean of ith participant
c_j = mean of jth rater