Good Clinical Practice: Considerations for Trials with Pragmatic or Decentralized Features

The public meeting will begin shortly
Due to the meeting size, please keep your microphone and video off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website soon after the meeting.

Please share your questions and comments for the speakers using the Zoom Q&A function.
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<td>Eric Lenze, MD</td>
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<td>8:25 am</td>
<td>Kenichi Nakamura, MD, PhD, MBA</td>
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<td>Moderated Discussion</td>
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<td>Closing Remarks &amp; Adjournment</td>
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Why Are We Here Today?

Understand the opportunities and challenges of conducting trials with innovative design features to help inform the development of responsive policies and guidelines that encourage innovation, while protecting participants and safeguarding the reliability of trial results.
Introduction

Khair ElZarrad, PhD, MPH

Director, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Eric Lenze, MD

Professor, Head of Psychiatry & Director
Healthy Mind Lab Washington University School of Medicine in St. Louis
This is what progress looks like: clinical trials in a remote world

Eric Lenze MD
Professor and Head of Psychiatry
Washington University School of Medicine, St Louis, MO
Good trials lead to scientific progress.
Improving speed and quality: fully-remote trials

**Problems**
- Studies are costly and slow
- Failure rate is high
- Study population is often inadequately diverse

**Solution:** fully-remote trial

**Benefits**
- Recruitment rate optimized
- Reduced burden for patients
- Expert site gains experience, continuously increasing quality

From: Lenze et al, Digital and precision clinical trials: innovations for testing mental health medications, devices, and psychosocial treatments. Neuropsychopharmacology 2023
Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression


Lenze et al, NEJM 2023
Fully-remote during COVID: the STOP COVID trials

Lenze et al., Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. JAMA 2020

Reiersen…& Lenze, The STOP COVID 2 study. Open Forum Infect Dis 2023
Fully-remote trials are now the norm.
Improving quality with precise measurement

**Problems**
- Measurement reliability is low
- Leads to study failure
- Barrier to demonstrating mediation, moderation

**Solution:** frequent, valid assessments

**Benefits**
- High measurement reliability
- Sample size requirements reduced
- Potential for precision medicine increased by well-powered mediation

From: Lenze et al, Digital and precision clinical trials: innovations for testing mental health medications, devices, and psychosocial treatments. Neuropsychopharmacology 2023
Infrequent, retrospective measurement is imprecise

Mofsen & Lenze, “When all else fails, listen to the patient: a viewpoint on the use of Ecological Momentary Assessment in Clinical Trials. JMIR Mental Health 2019

What has your energy been for the past week?

Hmm....

We rate an experience by its peak or end...

...not by its sum

time
Precise measurement with smartphone assessments

Kharasch & Lenze, Bioequivalence and Therapeutic Equivalence of Generic and Brand Bupropion in Adults With Major Depression: A Randomized Clinical Trial. Clinical Pharmacology & Therapeutics, 2019
Precise assessment in the STOP COVID trials

Patients self-monitored and entered their data.

Lenze et al., Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. JAMA 2020
How far we have gone: the LONG COVID trial
Summary: key points

- Fully-remote trials are the norm.
- Greater speed and quality are possible.
- This should accelerate scientific progress.
Craig Lipset, MPH

Co-Chair, Decentralized Trials & Research Alliance

Adjunct Professor, Rutgers

Vice President, Foundation for Sarcoidosis Research

Managing Partner, Clinical Innovation Partners
Considerations for Trials with Pragmatic or Decentralized Features: Perspectives on Decentralized Clinical Trials

Craig H Lipset
@craighlipset
12 September 2023
Craig Lipset: About Me

Board Member

- DTRA
- MedStar Health Research Institute
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Faculty

- Rutgers
- University of Rochester
- Empath Labs

Advisor

- Clinical Innovation Partners
- IMI
- TRIALS@HOME
- IEEE
- VULCÁN

Formerly

- Pfizer
- TransCelerate Biopharma Inc.
- PAREXEL
- Perceptive
- Adnexus Therapeutics

Views and positions expressed represent those of the presenter and not necessarily of the affiliations above.
“Decentralized?”

1. The jargon is not ideal
   The model is ‘decentralized’ for the site, but ‘centralized’ around the participant

2. Most other terms have their own limitations

3. But ‘decentralized’ is being used consistently…and globally

4. And the term does reflect a ‘truth’:
   trials have historically been “centered” at the site
   With only recent consideration to center participation around the participant
"Decentralized?"
Decentralized Clinical Trials [DCT]: Defined

Clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites

- Inclusive of hybrid and fully-remote
- Create optionality and choice

- May be at home
- Or may be pharmacy, community centers, local health providers, pop-up sites, mobile units, etc.

FDA Draft Guidance: “Decentralized Clinical Trials for Drugs, Biological Products, and 2 Devices” May 2023
### Decentralized Clinical Trials [DCT]: Defined

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
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<tbody>
<tr>
<td>FDA Draft Guidance</td>
<td>…some or all of the trial-related activities occur at locations other than traditional clinical trial sites.</td>
</tr>
<tr>
<td>May 2023</td>
<td></td>
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<tr>
<td>EMA Recommendations</td>
<td>…using procedures conducted outside the traditional ‘clinical trial site’.</td>
</tr>
<tr>
<td>December 2022</td>
<td></td>
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<tr>
<td>CTTI</td>
<td>… those in which some or all study assessments or visits are conducted at locations other than the investigator site via any or all …DCT elements.</td>
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<tr>
<td>DTRA</td>
<td>…utilizing technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site.</td>
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<tr>
<td>IMI Trials@Home</td>
<td>…make use of digital innovations and other related methods to make them more accessible to participants; by moving clinical trial activities to the participant’s home or to other local settings this minimises or eliminates physical visits to a clinical trial centre.</td>
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**Different words / Same themes:**
- Umbrella term inclusive of hybrid and fully-remote approaches
- Represents a collection of decentralized methods and tools (both processes and technologies)
- Focus on providing options for participation outside of a traditional “site”
Reasons to Decentralize Trials

**Patient Factors**
Experience & Access
Representation & Equity

**Business Continuity**
Maintaining trials in an unpredictable environment

**Sustainability**
Support Green Trials and ESG commitments
Leading Implementation Strategy: *Pairing DCT Toolkits to Study Needs*

1. Identify the decentralized research methods and tools needed by the medicine portfolio
   - eConsent
   - Video visits
   - Home health
   - Local labs+imaging
   - Remote monitoring
   - Digital endpoints
   - Central site/PI
   - Home drug supply

2. Pair the “right” method/tool to each study based upon diverse criteria
   - Patient insights
   - Drug delivery
   - Safety profile
   - Intelligence
   - Country requirements
   - Regulatory feedback
   - Environmental risk
   - Organizational culture
DCT1.0 → DCT 2.0

**DCT1.0**
- Clinic or home
- eConsent
- Video visits
- Home visits
- Limited remote monitoring
- Local specimens
- Supply chain home

**DCT2.0**
1. Locations beyond home...and the role of the HCP
2. Next gen participant support
3. Participant choice & flexibility
4. Site BYO-HIT
5. Patients BYO-RWD
6. Endpoint modernization
7. Platform revolution
8. Health systems as meta-sites
Decentralized Trials & Research Alliance

Non-profit collaboration

100 organizations

Exclusively focused on easing the global adoption of decentralized research methods

In order to improve trial access and participation for all
Centralized repository of resources (dtra.org)

Available for global research community

Inclusive of DTRA initiatives as well as publicly available solutions from partner organizations
Barriers to Scaled Adoption of Decentralized Trials

- Regulatory ambiguity
- Global variability
- Technology interop & data flow
- Investigator & patient readiness
- Endpoint limitations
- Organization culture
- Interstate licensing
Continuing Non-Linear Adoption

- Pre-Pandemic Experimentation
- Mid-Pandemic Adoption
- Post-Pandemic Hesitation
- Global Regulatory Decisions on 2020 Studies
- Ethical Imperative

Rate of DCT Adoption vs. Time
Considerations for Trials with Pragmatic or Decentralized Features: Perspectives on Decentralized Clinical Trials

Craig H Lipset
@craigm lipset
12 September 2023
Kenichi Nakamura, MD, PhD, MBA

Director, Department of International Clinical Development & Chief Management Officer, Clinical Support Office National Cancer Center Hospital
Fully decentralized clinical trials in oncology

Kenichi NAKAMURA, MD PhD MBA
National Cancer Center Hospital JAPAN
Why DCT in oncology area?

- **Regional disparity in clinical trial access**
  - Although multiple comprehensive genomic profiling tests can be used under national health insurance, only **9.1%** of patients can receive a matched drug.
  - Clinical trial access is limited for patients living in distant areas.
  - Some patients come to Tokyo to participate in clinical trials.

- Clinical trials for rare cancers or rare fractions are conducted only in big cities.
  - Patient advocacy groups have requested us to improve clinical trial access.

- Telemedicine for a new patient was allowed legally in response to the pandemic.
Fully decentralized clinical trial in oncology

Online visit by telemedicine
- Eligibility check
- Informed consent
- Drug shipment to patient’s home
- Go/No-go decision on treatment continuation
- Efficacy/safety evaluation

Perform delegated examinations
- Blood test, CT etc.
- Upload the results to DCT system

NCC is responsible for any clinical trial related activities

Delegation Contract
- Research funding will be paid
- Examination results are shared

Partner site
- No IRB review
- No EDC entry
- Remote monitoring

National Cancer Center (NCC)
- IRB review
- Assign PI/SI in NCC
- EDC entry
- Monitoring
- SAE reporting etc.

See the patient collaboratively with NCC
Benefits of full DCT in oncology

- **Better clinical trial access from a distant area**
  - Treatment options will be increased for patients undergoing CGP tests
  - Partner site is not a clinical trial site but a site that undertakes delegated tasks, so ethical review, education, and monitoring can be simplified

- **Faster patient accrual**
  - NCC can recruit patients not only from Tokyo but also from all over Japan
  - DCT has a high affinity for rare cancers and rare fractions where constant patient accrual is not always easy

- **Reduced clinical trial cost**
  - Cost up factor: Introduction of the DCT system
  - Cost down factors: Shortened accrual period, reduced monitoring costs
TAZETTA trial
Phase II investigator-initiated registration-directed trial for tazemetstat
If the result is positive, the drug indication of is expanded to the target disease

Planned sample size, 15 patients

- **Unresectable or metastatic epithelioid sarcoma(INI1-deficient)**
- Prior exposure: ≥ One chemotherapy include doxorubicin
- Age: 16-
- ECOG PS 0-2
- Measurable lesion etc.

**Delegated examinations to the partner sites**
- Blood testing, pregnancy test
- ECG, CT/MRI, Chest X-ray
- Echocardiography

Tazemetstat
800 mg BID, PO
28 days/course

**Primary Endpoint:**
PFS at w18 (Central assessment)

**Secondary Endpoint:**
PFS at w18 (PI assessment), PFS, OS, Duration of CR+PR, Disease control rate, Safety etc.

Patient accrual has started in Jan 2023 (4 Japan sites)
Good indication of DCT in oncology area

- Patient's symptoms are relatively stable
- Oral drug
- Less toxicity with sufficient safety information
- Rare cancers/rare fractions
- Endpoints can be collected remotely
  - In oncology, good indications of DCT are rare cancers and rare fractions using oral drugs with lower toxicity that are already approved, where the purpose is to expand drug indication
Telemedicine is conducted in the presence of the attending physician at the partner site.

- Touchpad is provided to the partner site with a telemedicine system installed.
- Patient gives eConsent by digital signature on touchpad.
- Investigational drug (oral) is delivered directly from NCC to the patient’s home.
- Examination results at the partner site are shared with NCC via eSource system.
DCT system between NCC and partner sites
1. Selection of partner sites

- **Current procedures**
  - NCC established **selection criteria for partner sites** to ensure patients’ safety
    - Hospitals designated by the government for cancer genomic medicine
    - Certain experiences of registration-directed trials
    - Having enough support staff for DCT
    - Having an emergency room
    - Having a consultation room with both EHR and internet connection etc.

  - Candidate sites are identified in advance, but **an official contract as the partner site is concluded AFTER an eligible patient appears**
    - Site set-up fee can be saved
    - Clinical trial information can be distributed in advance
1. Selection of partner sites

- **Discussion points**
  - What kind of tasks can be delegated to partner sites?
    - Is it possible to delegate examinations not performed in daily practice?
    - Is it possible to delegate invasive procedures (e.g. biopsy)?
    - Is it possible to delegate intravenous infusion as a part of protocol treatment?
  - To what extent does NCC need to give training/information to partner sites
    - e.g. should NCC provide investigator’s brochures to all partner sites every time it is updated?
  - What is the responsibility division point in an emergency situation?
2. eConsent

- **Current procedures**
  - NCC provides the partner site a touchpad site with the eConsent and telemedicine system installed
  - Physician/liaison at the partner site login the system prior to the start of IC process
  - Physician at the partner site sit aside to share medical information and put the patient at ease (D to P with D)
  - PI/SI at NCC makes a patient identification to check the patient’s ID card with a photo (e.g. driver’s license)
  - If the patient agrees to join the trial, the patient gives eConsent by digital signature on touchpad
  - Printed consent form is given to the patient

- **Discussion point**
  - Is multi-factor authentication required even when CRC ensures and records the process that patients themselves give eConsent?
3. Telemedicine

- **Current procedures**
  - Before each visit, the liaison at the partner site uploads the delegated examination results
  - CRC at NCC assures all the required examination results are surely shared
  - Telemedicine is performed using the touchpad
  - Even in telemedicine, the physician/liaison sits aside to share medical information and put the patient at ease (D to P with D)

- **Discussion point**
  - How to facilitate the scheduling of the three parties (patient, physician at the partner site, and PI/SI at NCC)
4. eSource

- Current procedures
  - Initially, it was difficult to share medical information on the Internet, and test results were shared by fax and CD-R
    - It was not easy to comply with the strict Japan’s medical information security guidelines
    - Timely information sharing with partner sites was a challenge
  - A new system is under development to securely share medical information on the Internet by providing a laptop PC with client certificates installed to partner sites and having test results uploaded from them

- Discussion point
  - Lack of a nationwide medical information-sharing system and the delay of the EHR standardization would hamper the spread of DCT in Japan
5. Direct drug shipment

- **Current procedures**
  - The pharmacy division in NCC makes a direct drug shipment to the patient’s home using a regular courier company
  - Temperature logger is enclosed with the shipped drugs
  - CRC at NCC remotely manages the number of residual drugs, and the patient sends the residual drugs as indicated at the next delivery of the investigational drugs

- **Discussion points**
  - Is direct drug shipment from the depot to the patient’s home possible under the supervision of the sponsor?
  - Can the delivery of investigational drugs to a patient’s home be outsourced to a regular courier company?
Regulatory guidance for DCT in Japan

- **eConsent**
  - Guidance for eConsent has been issued by the Ministry of Health, Labour and Welfare (MHLW) on March 30th, 2023
  - Patient authentication
  - Considerations of IT system, location, and procedures
  - Requirements for digital signature
  - Delivery of the consent form etc.

- **Other DCT guidance is under development by MHLW**
  - Partner sites
  - IT platform
  - Remote data acquisition
  - Direct drug delivery
Expectations for Annex 2

- **DCT in international trials**
  - DCT is expected to be utilized even in international clinical trials
  - It is likely that DCT systems are prepared and owned not by a sponsor but by an institution
  - Different DCT systems and procedures may be used in a single clinical trial by each country’s investigator/institution

- **Expectations for Annex 2**
  - It is expected that Annex 2 will include descriptions that promote high-level standardization so that DCT procedures in each country will not be much different
Cross-border DCT with Thailand

**Online visit by telemedicine**
- Eligibility check
- Informed consent
- Go/No-go decision on tx continuation
- Efficacy/Safety evaluation

**Perform delegated examinations**
- Blood test, CT etc.
- Upload the results to DCT system

**Delegation Contract**
- Research funding will be paid
- Examination results are shared

**Partner hospital**
- IRB review performed
- PI assigned
- Notification to TFDA
- Prescription of study drug
- No EDC entry
- Remote monitoring

**See the patient collaboratively with NCC**

**NCC**
- IRB review
- PI/SI assigned
- EDC entry
- Monitoring
- SAE reporting etc.

**NCC is responsible for all clinical trial related activities**
Medical license issue

- In principle, Japanese doctors who don’t have a medical license in Thailand cannot perform online medical care for patients living in Thailand.
- In a special circumstance, physicians with special skills are allowed to have a temporary license and practice medicine in Thailand under the supervision of Thai doctors.

- Thai MoPH and NCC agreed to issue a temporary medical license for medical oncologists at NCC engaged in DCTs.
MoU between Thai-MoPH & NCC

MoU has been concluded to promote cross-border DCTs
(June 14, 2023, Bangkok)
Differences from Japan’s domestic DCT

- **Differences**
  - Principal investigator should be assigned in Thailand
  - IRB review is required
  - IND application should be submitted to Thai FDA
  - Investigational drugs are prescribed from the partner site in Thailand

- **Benefits of cross-border DCT**
  - Cost of international trials would be significantly reduced
    - Remote monitoring is possible by sharing delegated examination results on the Internet
  - Clinical trial access for Thai patients is improved
  - Patient accrual is accelerated
Acknowledgment

- **DCT team at National Cancer Center Hospital**
  - Research Management Division
    - Hisahiro ITO, Tetsuya SASAKI, Kanako KONDO, Kaori IZUMINO, Satoshi KAWASHIMA, Mamiko KAWASAKI, Naoko SO, Sachie KAWABATA, Natsuko OKITA
  - Clinical Research Coordinating Division
    - Miki ITO, Chie MIYANO, Mari TAKAHASHI, Sho MURATA, Chiharu NAKANO, Ran KOHARA, Hiroko NAKAHAMA
  - Pharmacy Division
    - Makoto MAEDA
  - Medical Affairs Division
    - Kenji UNAI

- **Collaborators at the partner sites**
  - Shinjiro AOGI  Shikoku Cancer Center
  - Kenji TAMURA  Shimane University Hospital

- **Collaborators in Thailand**
Discussion

Moderator
Khair ElZarrad, PhD, MPH

Panelists
Eric Lenze, MD
Craig Lipset, MPH
Kenichi Nakamura, MD, PhD, MBA
Thank You!