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

The public meeting will begin shortly

September 12-13, 2023, from 7:30-9:30 am ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

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.

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

7:30 am	Welcome & Overview
7:35 am	Introduction
7:45 am	Eric Lenze, MD
8:05 am	Craig Lipset, MPH
8:25 am	Kenichi Nakamura, MD, PhD, MBA
8:45 am	Moderated Discussion
9:25 am	Closing Remarks & Adjournment

Why Are We Here Today?

REAGAN-UDALL FOUNDATION FOR THE FDA

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.

REAGAN-UDALL FOUNDATION FOR THE FDA

Introduction

Khair ElZarrad, PhD, MPH

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

REAGAN-UDALL FOUNDATION for the 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.


Try
Fail
Try
Again
SUCCESS

Improving speed and quality: fully-remote trials

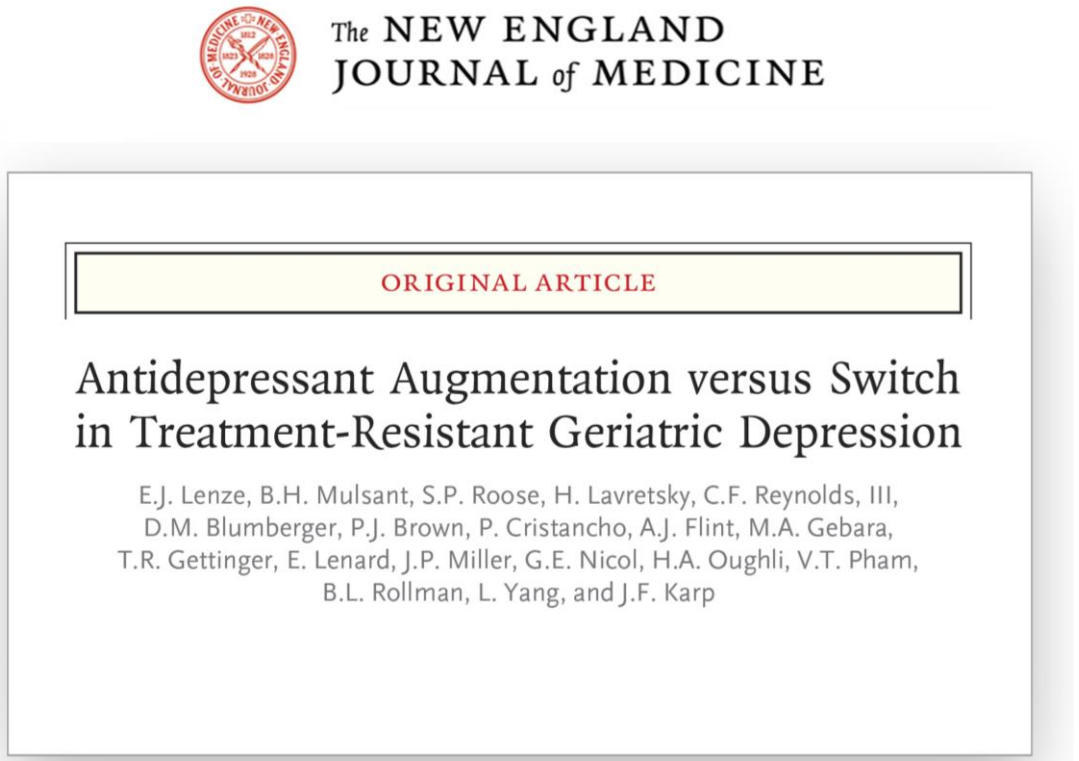
Problems
- Studies are costly and slow
- Failure rate is high
- Study population is often inadequately diverse

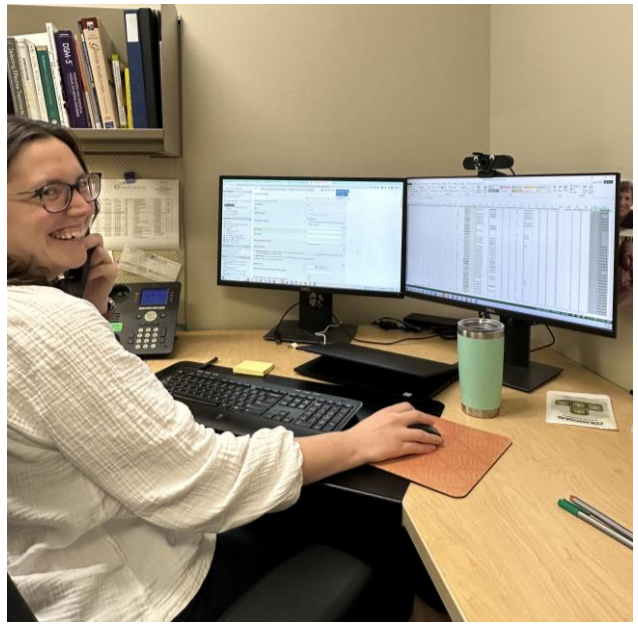
Solution: fully-remote trial

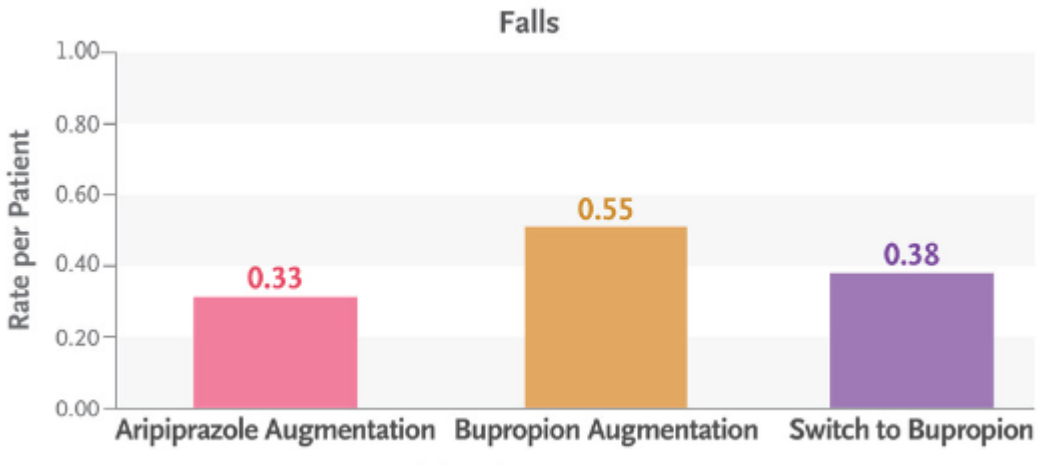
Benefits
- Recruitment rate optimized
- Reduced burden for patients
- Expert site gains experience, continuously increasing quality

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

Fully-remote participants in a clinical trial

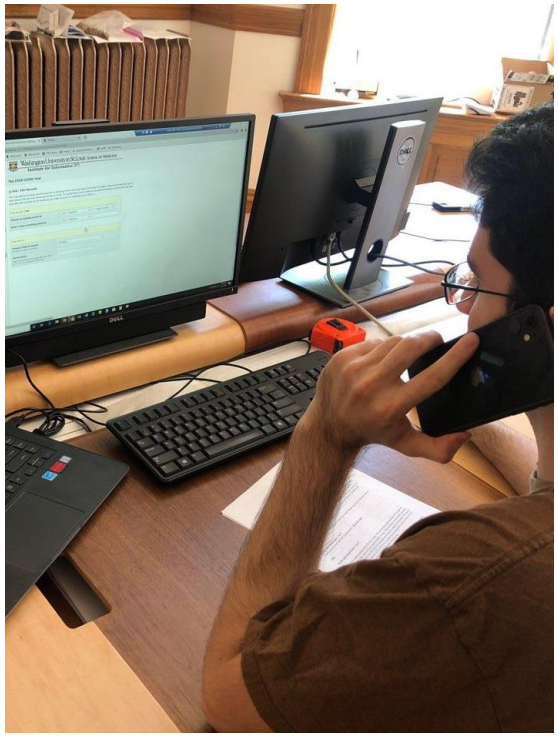


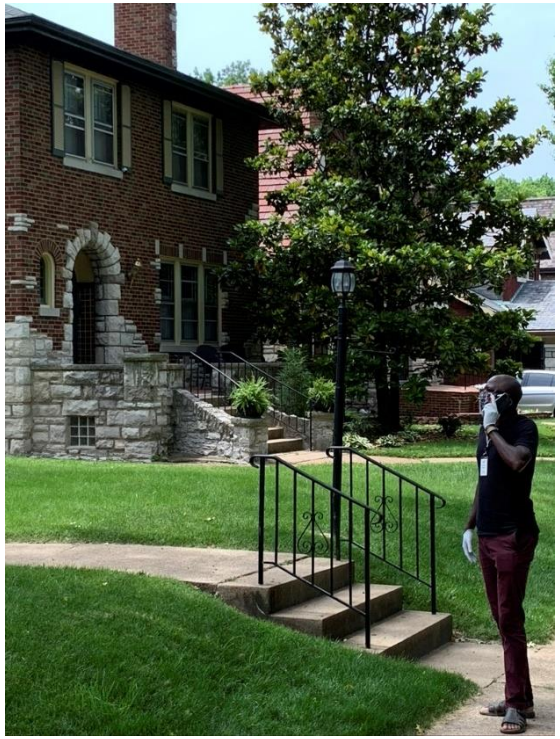




Lenze et al, NEJM 2023

Fully-remote during COVID: the STOP COVID trials

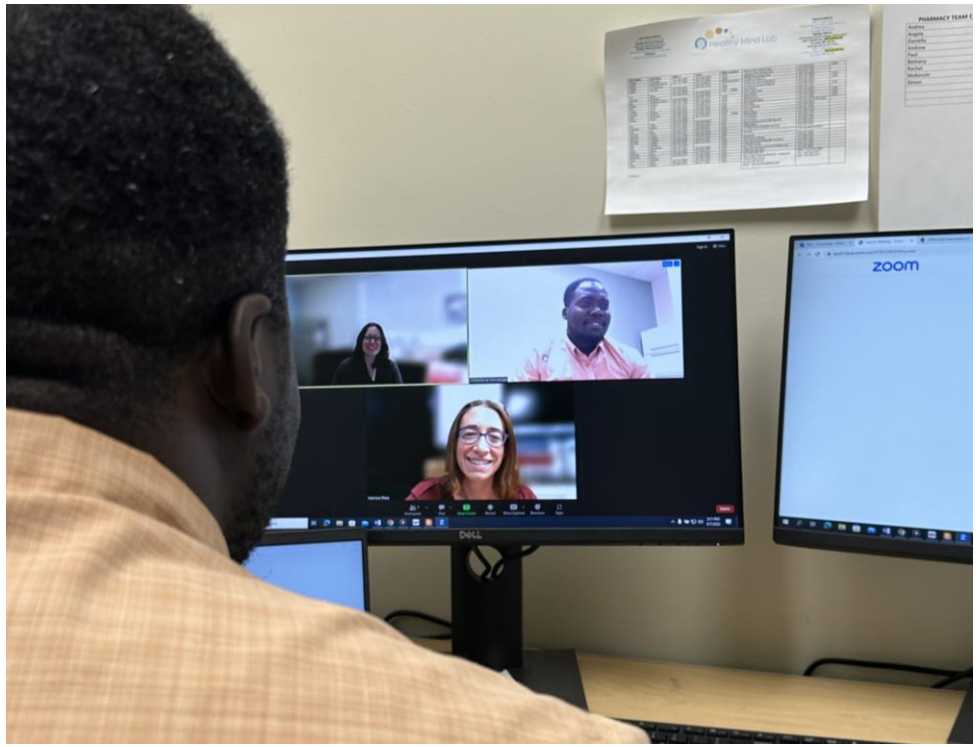




Lenze et al., Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. JAMA 2020

Reiersen…& Lenze, The STOP COVID 2 study. Open Forum Infect Dis 2023

Fully-remote trials are now the norm.



Washington University School of Medicine in St. Louis

DEPARTMENT OF ANESTHESIOLOGY AND DEPARTMENT OF PSYCHIATRY

Center for Perioperative Mental Health

Improving quality with precise measurement

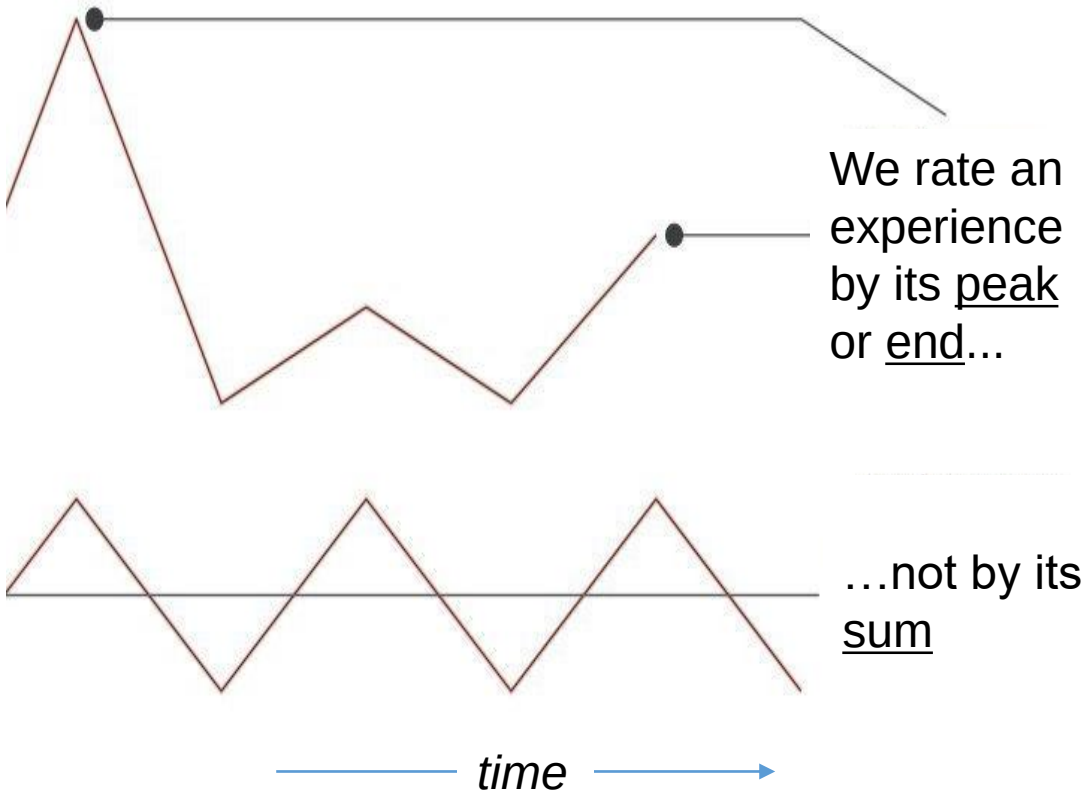
Problems
- Measurement reliability is low
- Leads to study failure
- Barrier to demonstrating mediation, moderation

Solution: frequent, valid assessments

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

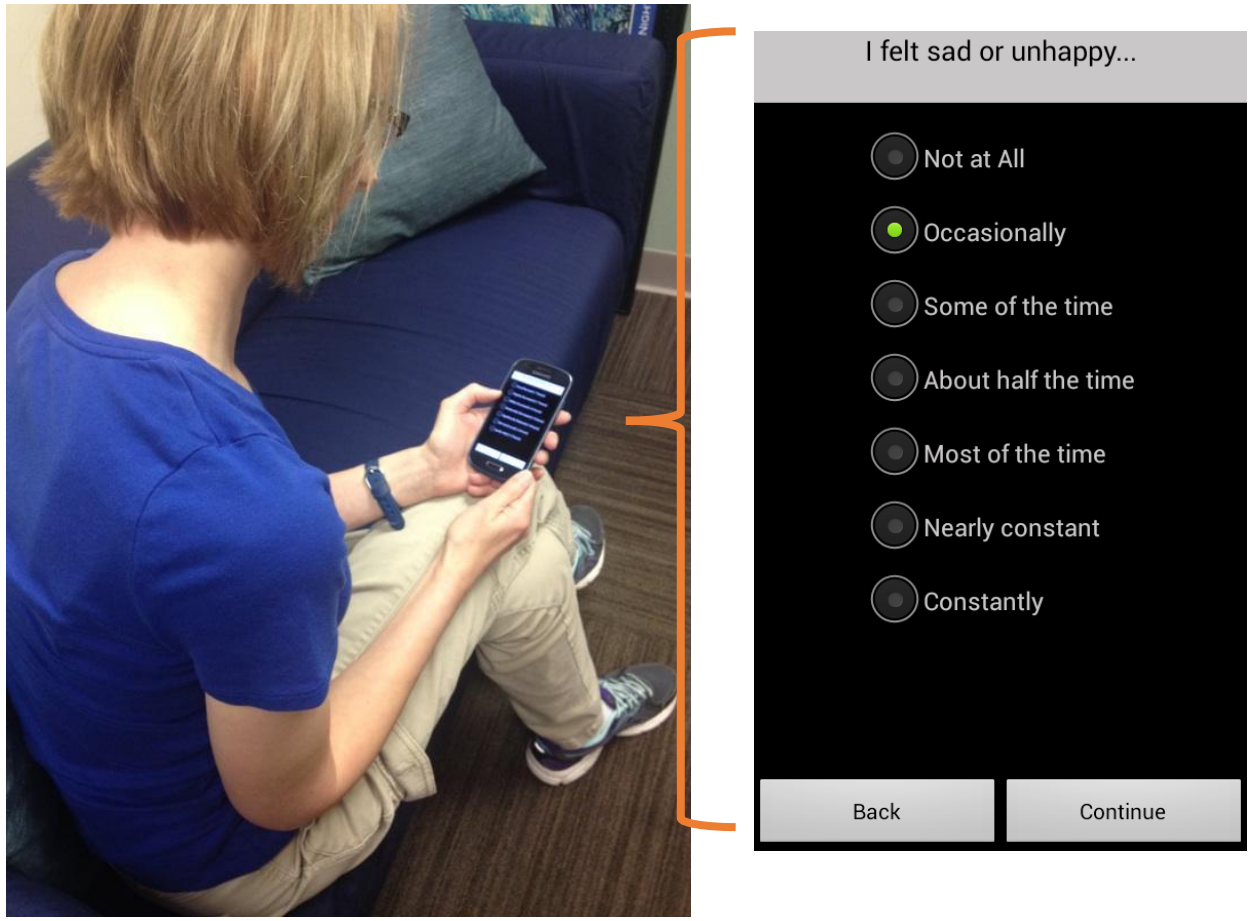
From: Lenze et al, Digital and precision clinical trials: innovations for testing mental health medications, devices, and psychosocial treatments. Neuropsychopharmacology 2023

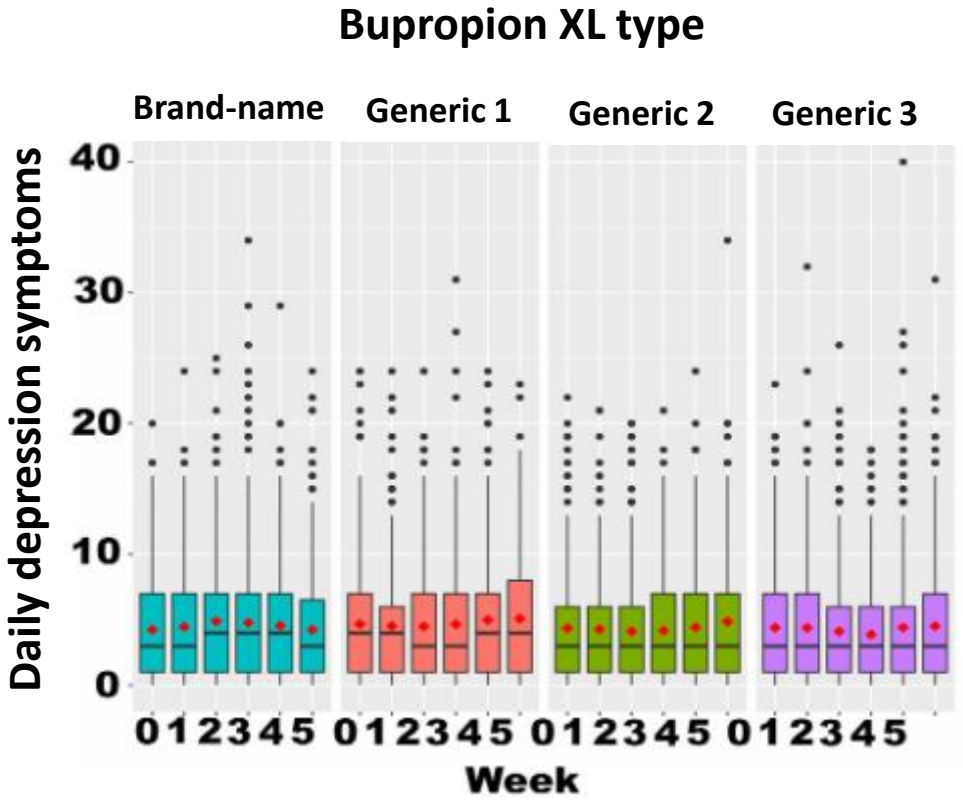
Infrequent, retrospective measurement is imprecise



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

Precise measurement with smartphone assessments



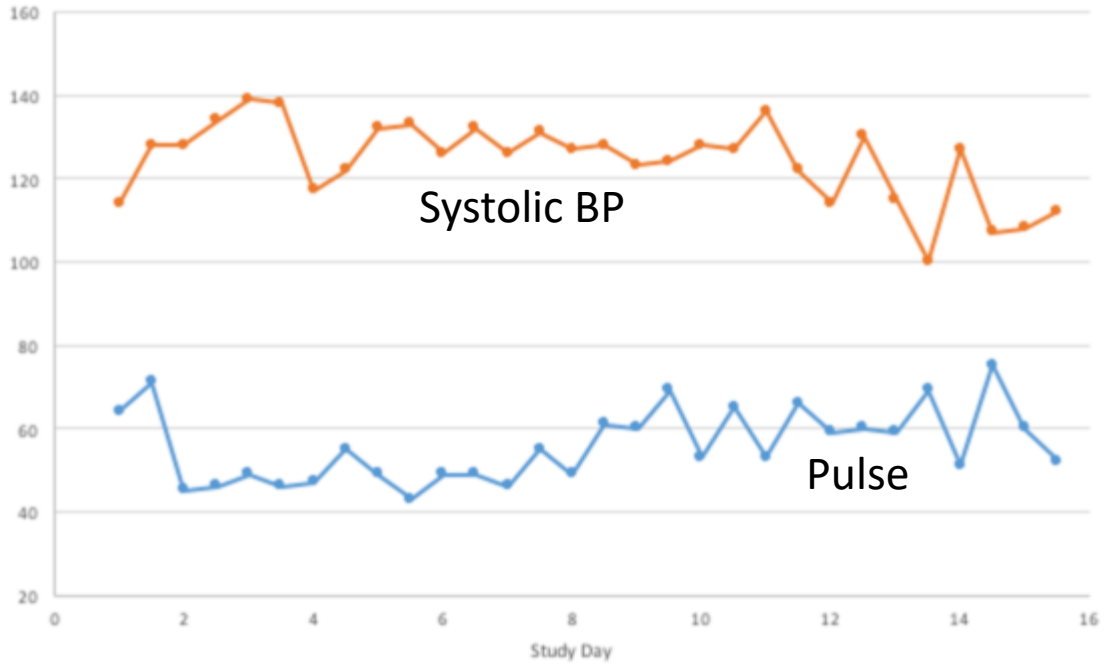


Kharasch…& Lenze, Bioequivalence and Therapeutic Equivalence of Generic and Brand Bupropion in Adults With Major Depression: A Randomized Clinical Trial. Clinical Pharmacology & Therapeutics, 2019

Precise assessment in the STOP COVID trials

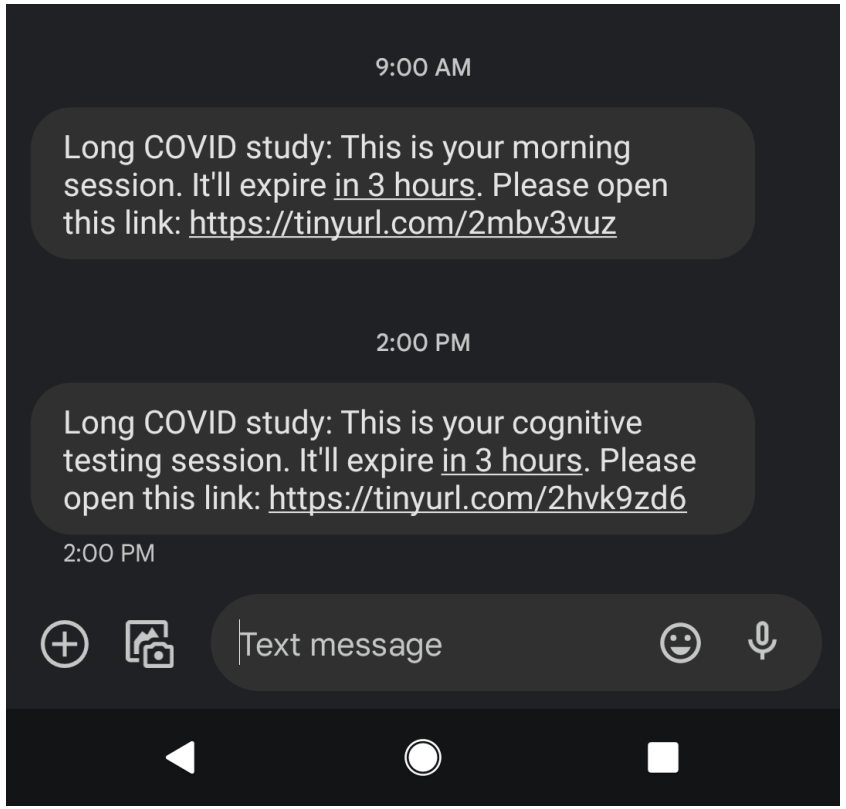
Patients self-monitored and entered their data.

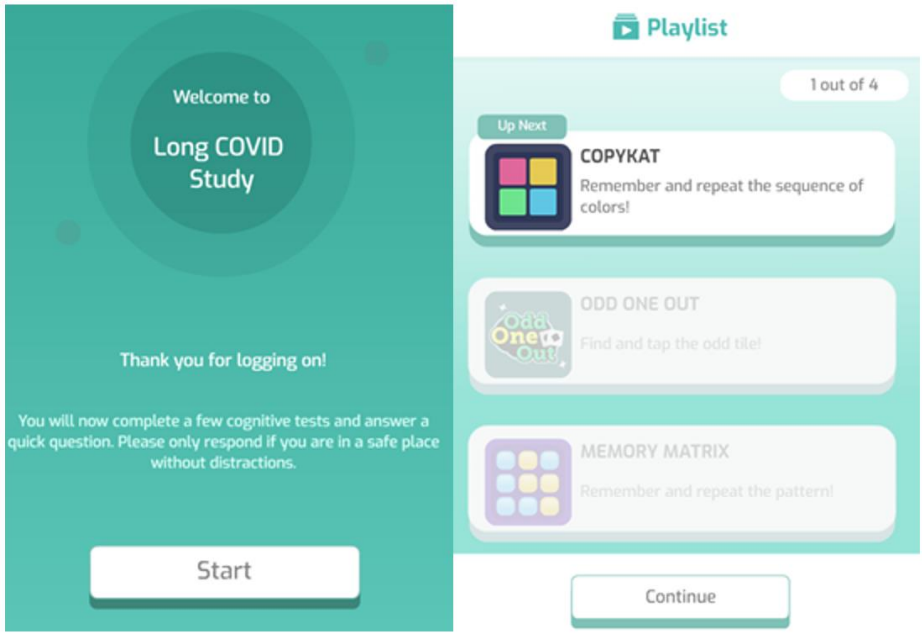
One participant's vital signs in the study

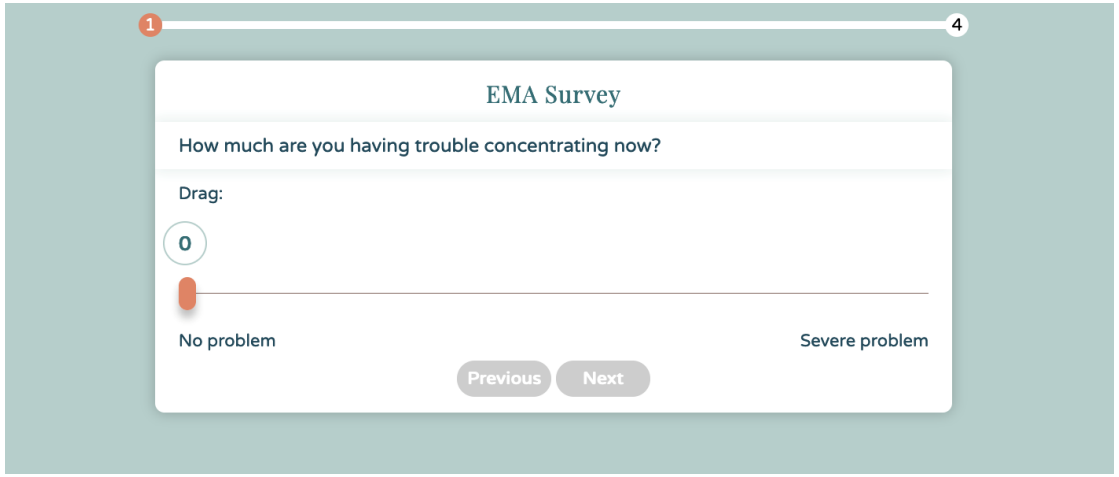


Lenze et al., Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. JAMA 2020

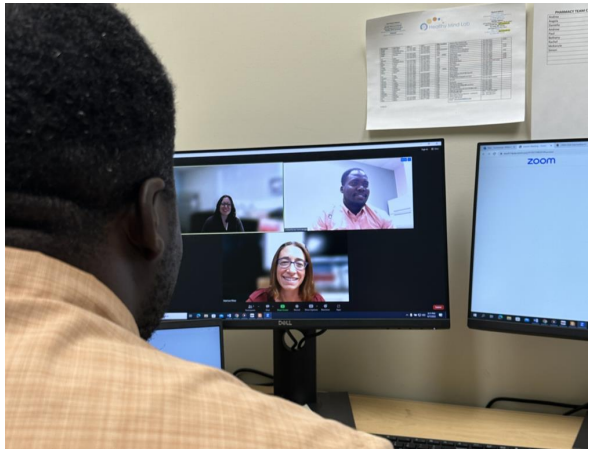
How far we have gone: the LONG COVID trial







Summary: key points



Fully-remote trials are the norm.

Greater speed and quality are possible.

This should accelerate scientific progress.

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

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
@craiglipset
12 September 2023

Craig Lipset: About Me

Board Member

DTRA Decentralized Trials & Research Alliance

MedStar Health Research Institute

FSR Foundation for Sarcoidosis Research

Circuit Clinical

Empath Labs

MedVector

Faculty

Rutgers

University of Rochester

Advisor

Clinical Innovation Partners

imi

Trials @ Home

IEEE Advancing Technology for Humanity

Vulcan HL7 FHIR

Formerly

Pfizer

TransCelerate BioPharma Inc.

Parexel perceptive Informatics

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**
   ~~*Virtual. Distributed. Remote.*~~

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 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)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

May 2023
Clinical/Medical

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

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

National Principles for Teletrials in Australia

Based on the International Council for Harmonisation Guideline for Good Clinical Practice

ICH E6 (R2)

ew Drugs and Clinical Remedies. Core

nline First Publishing Date: 2022-06-20 08:27:40 Online First Certificate Download

Expert consensus on remote intelligent clinical trials Online First English Full Text (MT)

Zhang Jing Li Gaoyang

us on Remote Intelligent Clinical Trials" Compilation Expert Group Shanghai Pharmaceutical Association Drug Clinical Research Professional Committee Drug Information Association China Digital Health Community

ve> remote intelligent clinical trials (decentralized & digitalized clinical trials, DCT) is a kind of implementation of the "subject-centered" concept, not limited to decentralized), relying on digital (digitalized) and other innovations A new type of clinical trial conducted by science and technology.

Taiwan Published Guidelines for Decentralized Measures for the Implementation of Drug Clinical Trials

POSTED ON 26TH JUNE 2023 BY REGASK

Food and Drug Administration published Guidelines for Decentralized Measures for the Implementation of Drug Trials. Below is a summary of the guidelines:

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

FDA Draft Guidance: "Decentralized Clinical Trials for Drugs, Biological Products, and 2 Devices " May 2023

- 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.

Decentralized Clinical Trials [DCT]: Defined

Source	Definition
FDA Draft Guidance May 2023	…some or all of the trial-related activities occur at locations other than traditional clinical trial sites.
EMA Recommendations December 2022	…using procedures conducted outside the traditional 'clinical trial site'.
CTTI	… 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.
DTRA	…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.
IMI Trials@Home	…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.

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

eConsent
Video visits
Home health
Local labs+imaging

Remote monitoring
Digital endpoints
Central site/PI
Home drug supply

- Identify the decentralized research methods and tools needed by the medicine portfolio
- Ensure aligned SOPs & training, identify new partners, modify protocols/templates

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

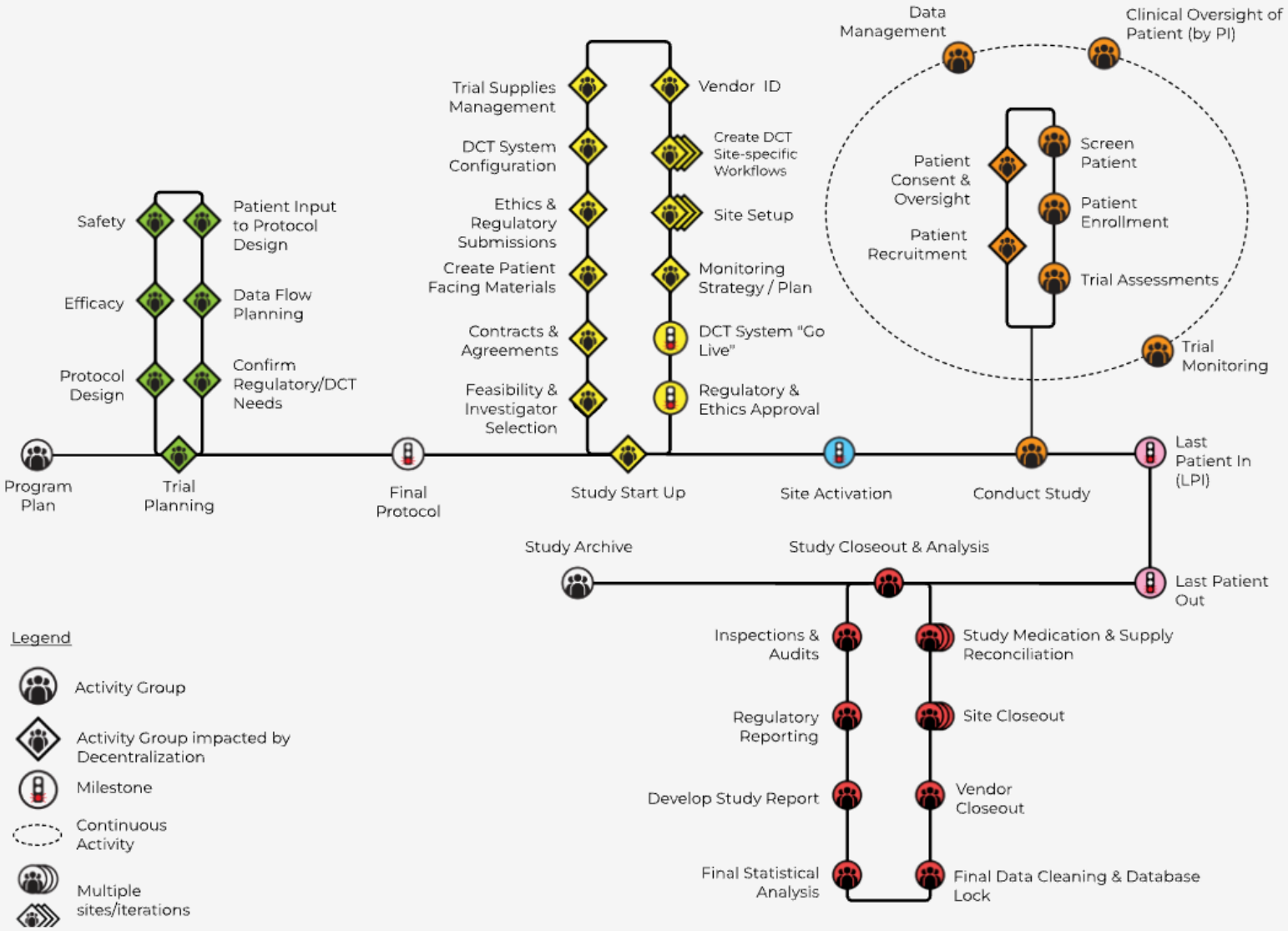
In order to improve trial access and participation for all

Decentralized Trials & Research Alliance

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

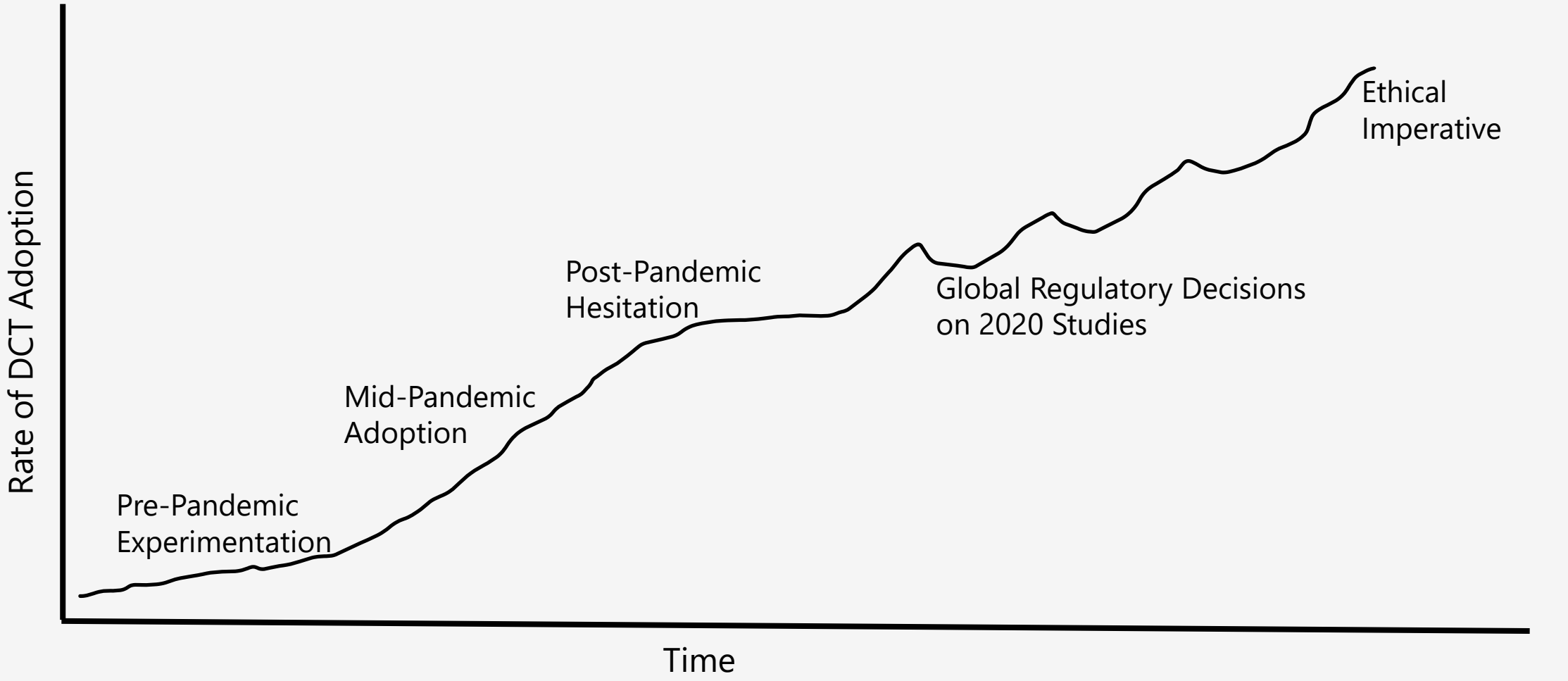
Endpoint limitations

Organization culture

∧

Interstate licensing

Continuing Non-Linear Adoption



Considerations for Trials with Pragmatic or Decentralized Features:

Perspectives on Decentralized Clinical Trials

Craig H Lipset
@craiglipset
12 September 2023

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Kenichi Nakamura, MD, PhD, MBA

Director, Department of International Clinical Development & Chief Management Officer, Clinical Support Office
National Cancer Center Hospital

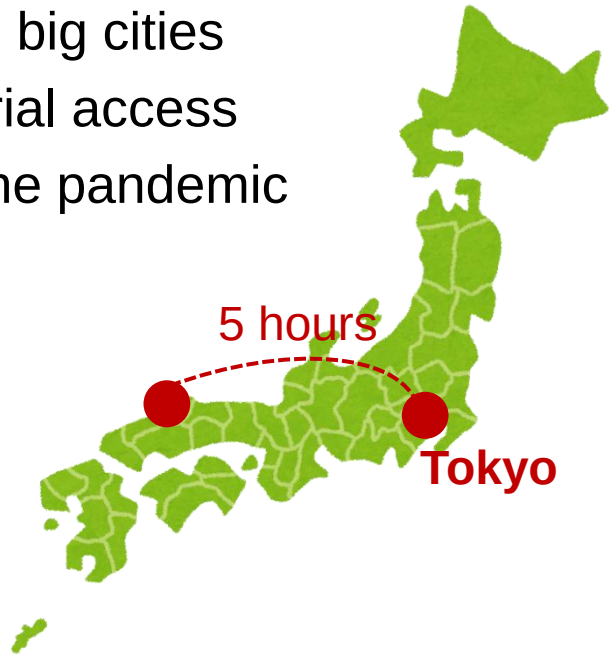
Fully decentralized clinical trials in oncology

Kenichi NAKAMURA, MD PhD MBA
National Cancer Center Hospital JAPAN

National Cancer Center 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

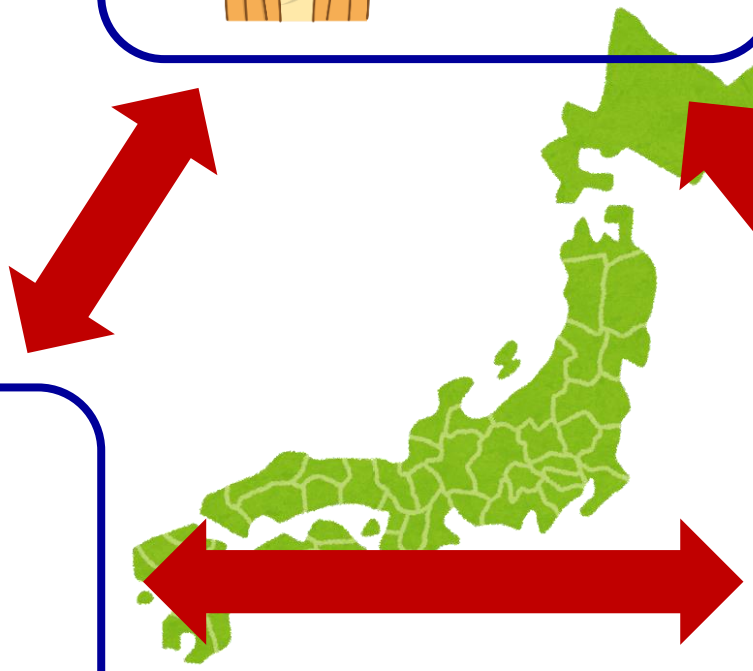
Patient living
in distant area

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

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.

Delegation Contract

- ✓ Research funding will be paid
- ✓ Examination results are shared

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.

Tazemetstat
800 mg BID,PO
28 days/ course

Delegated examinations to the partner sites

Blood testing, pregnancy test
ECG, CT/MRI, Chest X-ray
Echocardiography

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

Partner site at distant area

Patient

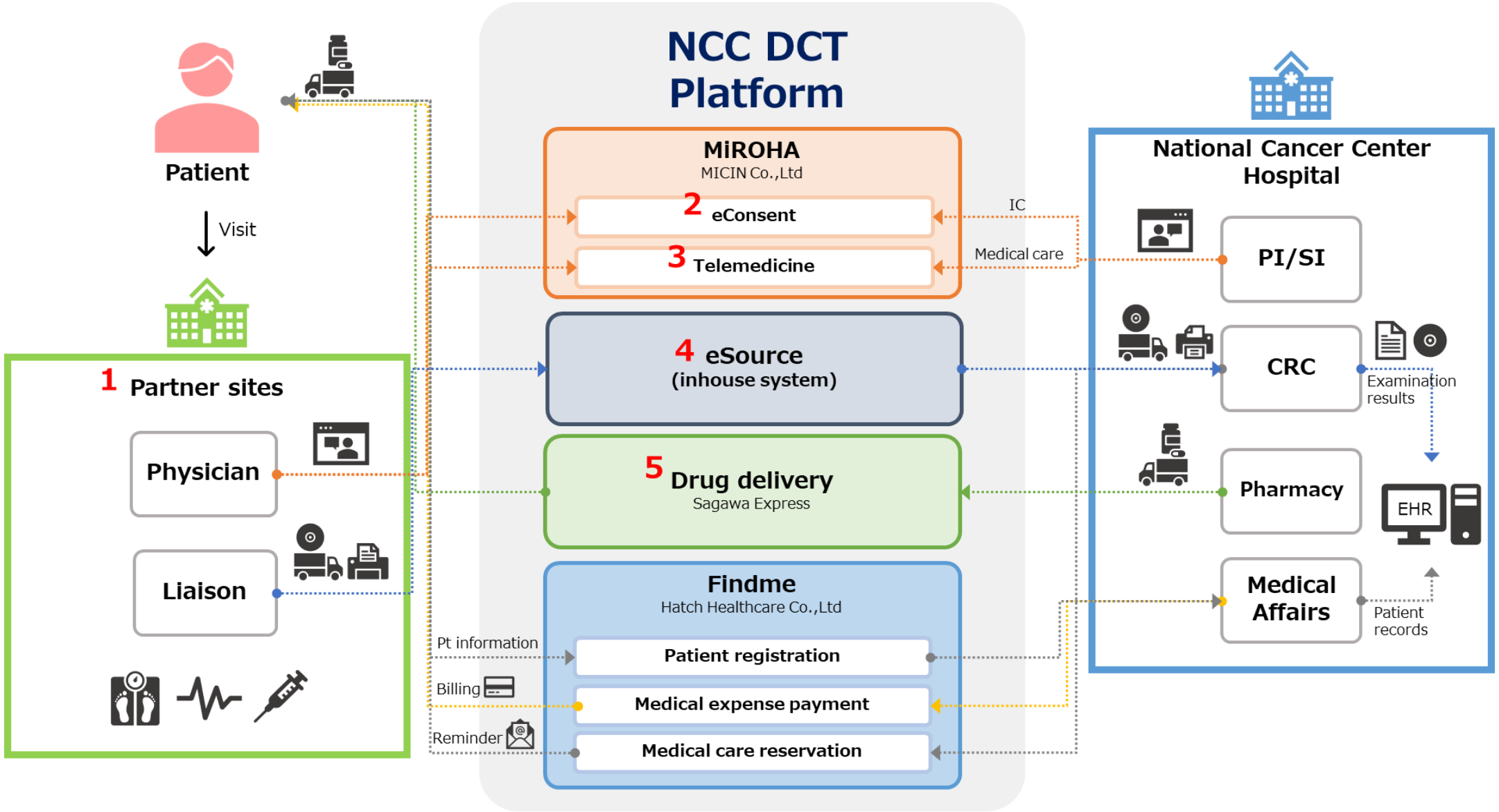
Physician

National Cancer Center

Investigator (GCP)

- ✓ 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)

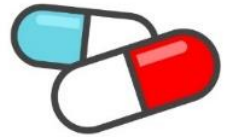
- Discussion point
  - How to facilitate the scheduling of the three parties (patient, physician at the partner site, and PI/SI at NCC)

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

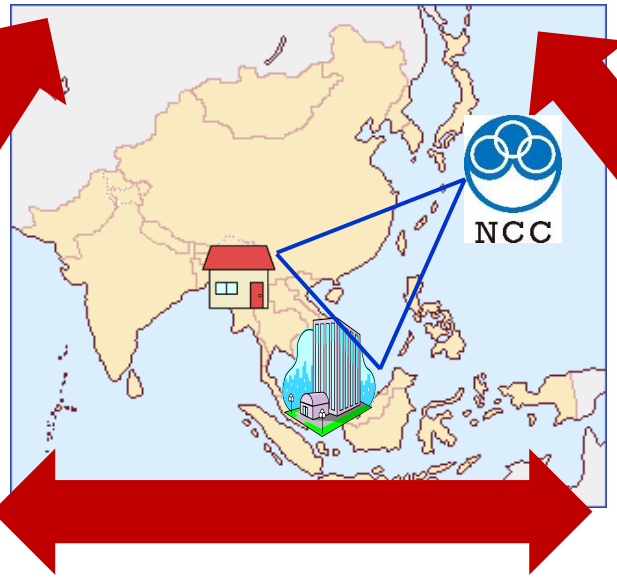
- Expectations for Annex 2
  - It is expected that Annex 2 will include descriptions that promote high-level standardization so that DCT procedures in each country will not be much different

Cross-border DCT with Thailand

Patient living in 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



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

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

NCC

IRB review
PI/SI assigened
EDC entry
Monitoring
SAE reporting etc.

NCC is responsible for all clinical trial related activities

Difficulty: cross-border DCT

- 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 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

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Discussion

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Moderator

Khair ElZarrad, PhD, MPH

Panelists

Eric Lenze, MD

Craig Lipset, MPH

Kenichi Nakamura, MD, PhD, MBA

Thank You!

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