Decentralized Trials- From Guidance to Reality & What's Left

Adrian Hernandez, Director, Duke Clinical Research Institute
Pamela Tenaerts, Chief Scientific Officer, Medable
Craig Lipset, Co-Chair, Decentralized Trials & Research Alliance

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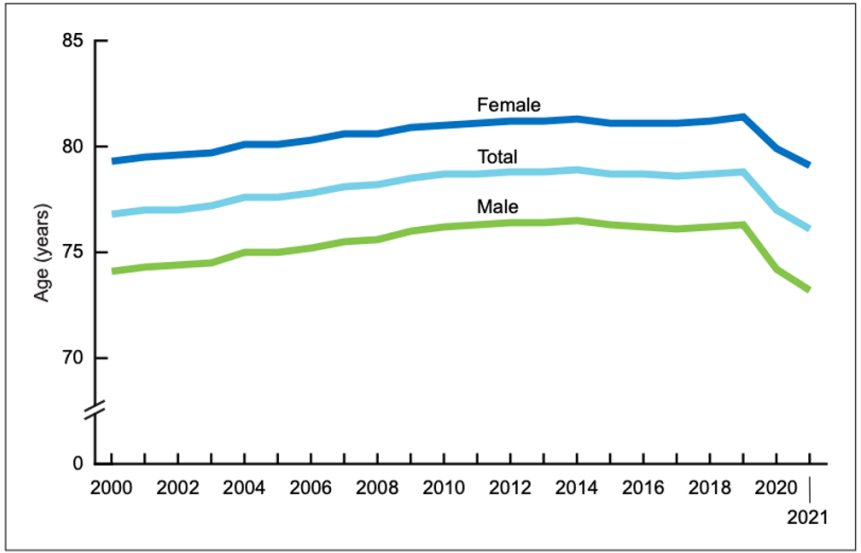
Agenda

- Why care?
- Guidance for all?
- Are we ready?
- What's left?

Why care?

- Science & Health
  - Speed of Science
  - Questions >> Answers
- Patient/Participant Factors
  - Experience
  - Access
  - Diversity & equity
- Environment & Business
  - Greener trials
  - Unpredictable world
- We're losing years of life



NOTES: Estimates are based on provisional data for 2021. Provisional data are subject to change as additional data are received. Estimates for 2000–2020 are based on final data.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

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Reminder:
What's the Problem We're Aiming To Solve?

~2% **~85%**

McHugh, K., Swamy, G., & Hernandez, A. (2018). *Journal of Clinical and Translational Science, 2*(6), 384-392. doi:10.1017/cts.2019.1

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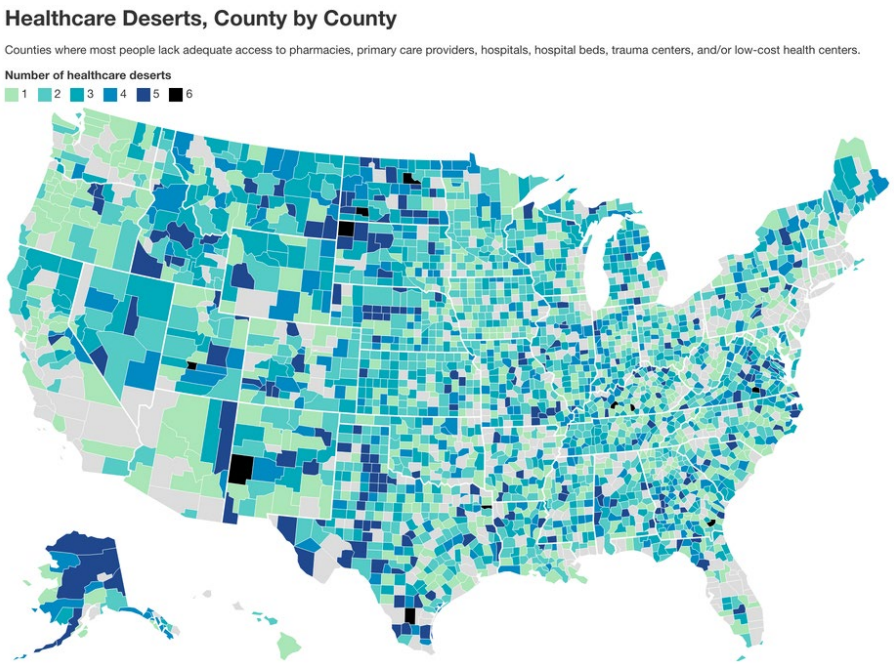
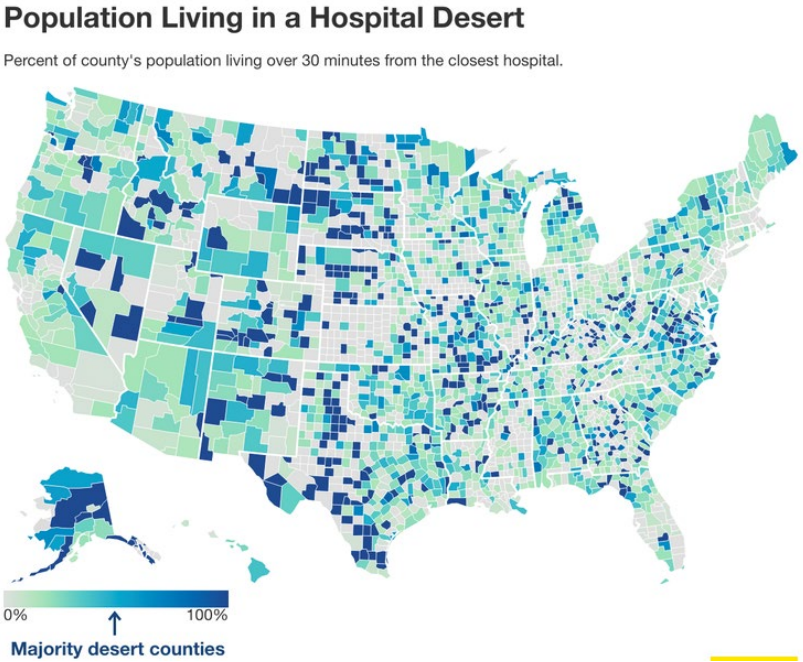
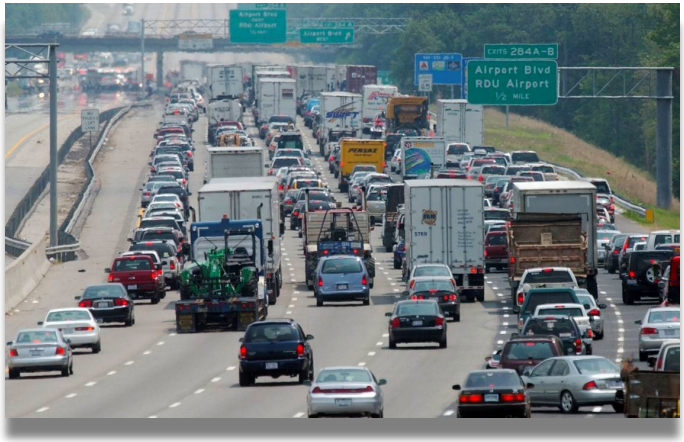
Covering Clinical Trial Deserts





Have you been a TRIAL participant?

And who can or would again?



CASE EXAMPLE

ACTIV-6

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What is ACTIV-6?

A STUDY TO HELP PEOPLE WITH MILD-TO-MODERATE COVID-19 FEEL BETTER FASTER

@ACTIV6study

ACTIV-6 is part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, which was created to speed the development of effective treatments and vaccines for COVID-19.

What are we trying to find out together?

How can we help people with COVID-19 feel better faster?

How can we prevent people with COVID-19 from going to the hospital?

How do we share what we are learning?

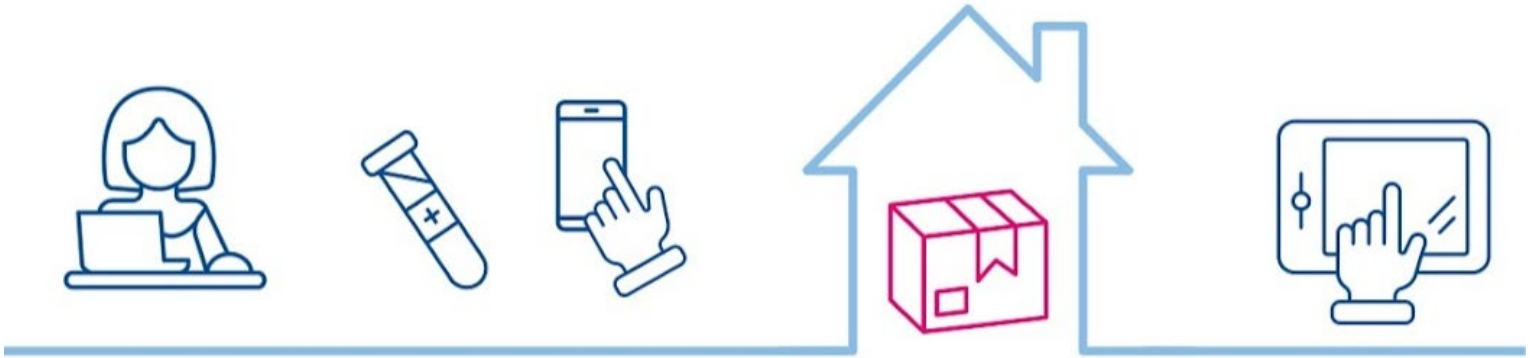
Visit activ6study.org for study results and the latest news.

What makes ACTIV-6 different?

ACTIV-6 is testing several medications that are approved to treat conditions other than COVID-19 and can be found at your local pharmacy. This provides options to participants and helps generate results faster.

Participate from home — study medication is mailed directly to participants who can sign up and complete surveys online or over the phone.

How does the study work?



Learn about ACTIV-6 online, on the radio, or from health systems, pharmacies, testing centers, or community partners.

Test positive for COVID-19.

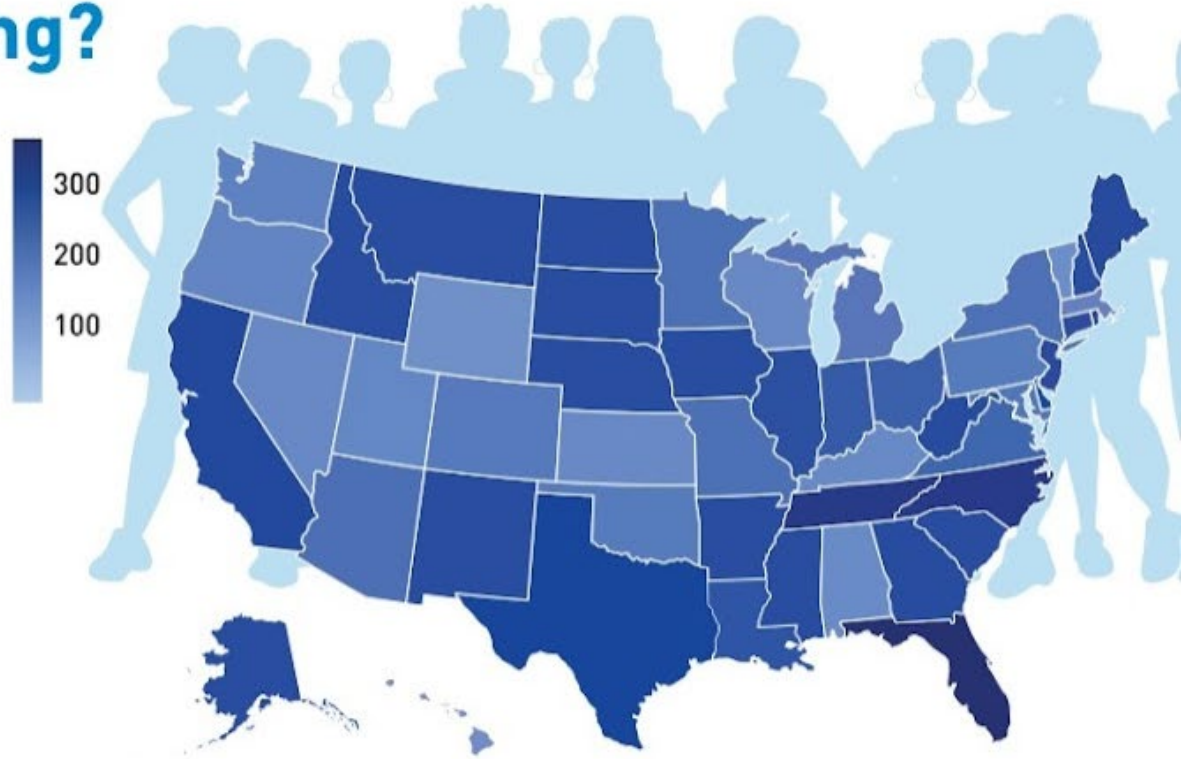
Enroll online or over the phone. activ6study.org

Receive assigned study medication and directions at home. **Take** the study medication as directed.

Complete surveys about how you feel online or over the phone.

Who is participating?

- All 50 US States
- 93 sites
- >7000 randomized
- RANDOMIZATION 60->400 WEEK
- 5 Arms Completed
- 1 Arm ENROLLED
- 1 Arm ON LAUNCH PAD



ACTIV-6

@ACTIV6study

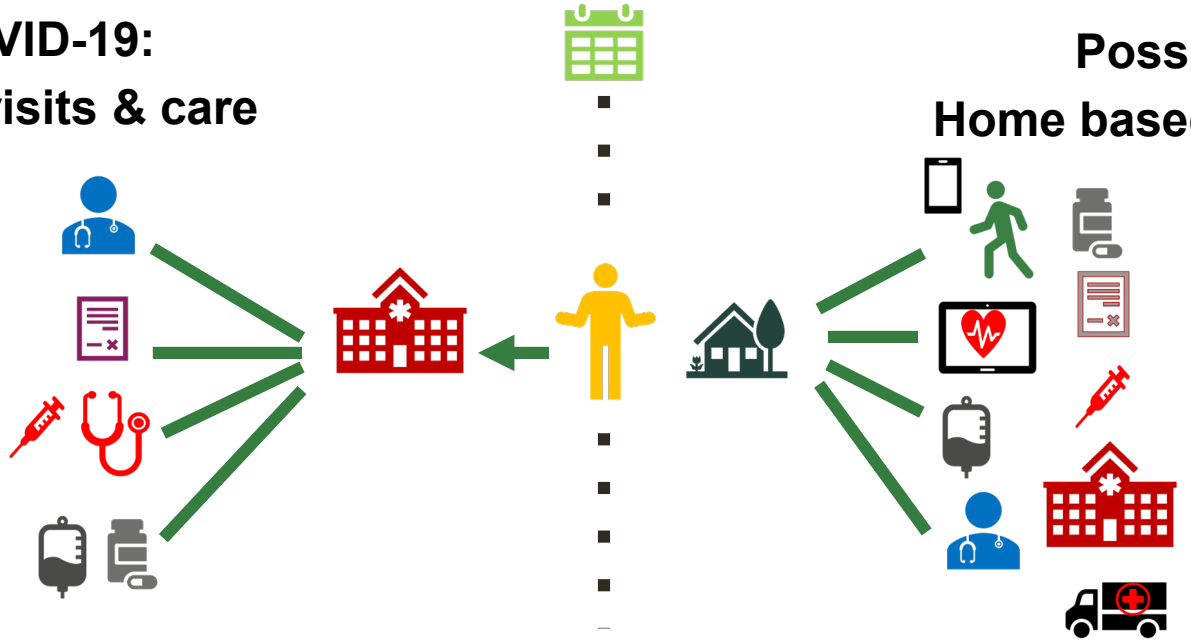
A Changed World of Possibilities: Pre-Covid to Post COVID

Pre-COVID-19:

Site based visits & care

Possibilities:

Home based visits & care



CTTI

https://ctti-clinicaltrials.org/our-work/digital-health-trials/running-a-decentralized-trial/

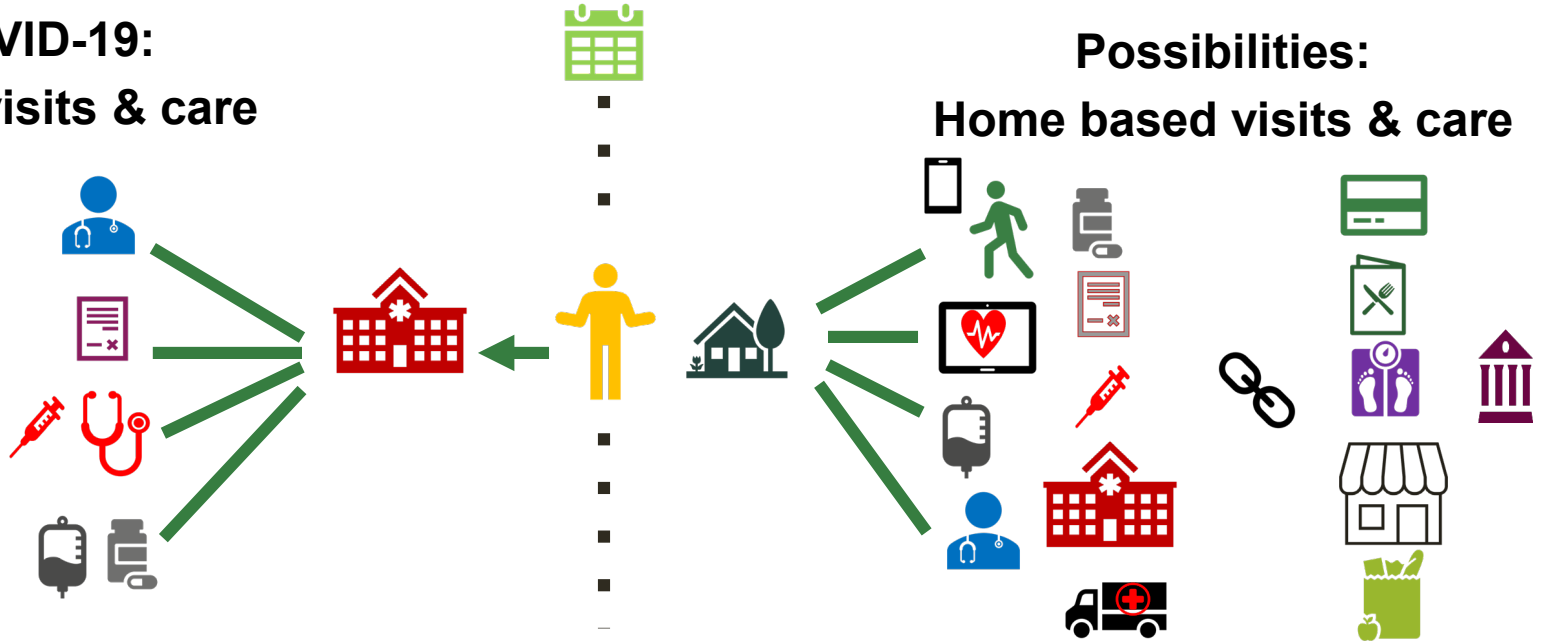
A Changed World of Possibilities: Pre-Covid to Post COVID

Pre-COVID-19:

Site based visits & care

Possibilities:

Home based visits & care



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DCT-Specific Regulatory Guidance

Beyond the Pandemic Guidance Documents

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

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

September 2021
Version 2.0
T +45 4488 9123
E kf@dkma.dk

The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products

National Principles for Teletrials in Australia

Based on the International Council for Harmonisation Guideline for Good Clinical Practice
ICH E6 (R2)

Chinese Journal of New Drugs and Clinical Remedies. Core

(Accepted Version) Online 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

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

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

swissmedic swissethics

Position Paper on decentralised clinical trials (DCTs) with medicinal products in Switzerland

(Version 2.0, 15 December 2022)

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

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

We act for public and animal health

Start / Permission, approval and control / Clinical trials / Products for human use / Decentralised clinical trials

Clinical trials

Products for human use

Clinical Trials Regulation EU 536/2014

Clinical trials – according to Directive 2001/20/EC

Clinical trials and GCP – according to Directive 2001/20/EC

Decentralised clinical trials

Published: June 18, 2021
Last updated: December 19, 2022

Conducting clinical trial in a decentralised setting could facilitate subjects' participation. Procedures in the trial could then be carried out outside the traditional trial site and with use of digital tools.

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

POSTED ON 26TH JUNE 2023 BY REGASK

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

Draft Guidance: DCTs

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.

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Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders
Recommendations Due August 1st

- The FDA is seeking feedback on newly released draft guidance providing about the conduct of decentralized clinical trials (DCTs)
- FDA notes benefits of DCTs as:
  - Promoting research participation in areas where there are limited or no traditional clinical trial sites
  - Making participation easier for study participants – participate from home and reduce travel and other burdens
  - Or, participate at a local clinic, pharmacy, or remotely (home visit, telehealth, wearables) to ensure convenience and comfort
- Fully decentralized approaches may be best for studies with well-established safety profiles, while hybrid approaches may be better for those requiring complex or follow-up assessments

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FDA Draft DCT Guidance: Key Themes (1/4)

- DCTs are clinical trials – the **same rules** and expectations for patient safety and data integrity apply.
- A **physical location** should be listed on the 1572 to support inspections.
- DCTs may involve a **network of locations** (where trial personnel and local HCPs work and where trial-related services are provided) all under the oversight of the PI.
- **HCPs** (doctors or nurses who are not trial personnel) may perform trial-related activities (including on a fee-for-service basis) including routine care activities that do not require detailed knowledge of the protocol or IP:
  - These may take place at the participant's location or another healthcare facility
  - Video and other technology may help with investigator oversight
  - HCPs are listed on a Task Log and not on the 1572
  - They may enter data into an eCRF (and be listed as an authorized data originators) or can upload forms to be entered by other trial personnel; Investigators must regularly review this data

FDA Draft DCT Guidance: Key Themes. (2/4)

- Differences in variability and precision of data obtained directly by participants or from HCPs may impact **non-inferiority trials**.
- The protocol should **specify** for which visits **telehealth** is appropriate and which should be seen **in-person** (although this is not specifically called out for in-home visits).
  - Investigators should confirm participant **identity** with each remote visit
  - State/regional **telehealth laws** apply
- Digital Health Technology (**DHT**) use should refer to DHT draft guidance and efforts must ensure use of technology is available and suitable for use by all participants.
- The **protocol** should describe DCT operational aspects such as:
  - Scheduled and unscheduled clinical trial visits (remote and in-person, as applicable)
  - Transmission of reports on activities performed at different locations
  - Delivery and return of IP to/from trial participants (and accountability if applicable), and how physical integrity and stability of the IP will be maintained during shipment
  - Safety monitoring and management of adverse events

FDA Draft DCT Guidance: Key Themes (3/4)

- **Investigators** should enroll only as many trial participants as they can appropriately manage to ensure adequate supervision of DCT-related activities.
- **Consent** may be obtained remotely with a process reviewed by the IRB.
  Consent must include contact details for questions as well as describe who will have access to a participant's personal health data during the trial.
- **Telehealth** and real-time video interactions are considered a "live exchange of information between trial personnel and trial participants" and not considered electronic records therefore not subject to 21CFR Part 11 (privacy and security should be ensured and visits must be documented)
- Remote trial personnel or HCPs **may administer IP** with well-characterized safety and where specialized monitoring is not required after dosing
  - Drugs best suited for home-delivery include long shelf-life and good stability profiles
  - Drugs may be shipped to locations other than the site with specialized handling, shipping and storage conditions
  - Central distribution for IP to participant may be used with trial personnel controlling release and monitoring receipt/return

FDA Draft DCT Guidance: Key Themes (4/4)

- Additional considerations are needed for:
  - **Data Management Plan**: Data origin and data flow from all sources; Methods for remote data acquisition; List of vendors for data collection, handling and management
  - **Monitoring Plan**: Specify frequency of record and source doc review; Note unique considerations; Encourage use of centralized and risk-based approaches
  - **Safety Plan**: How AEs identified remotely will be evaluated and managed; Participants must be able to contact trial personnel to report AEs, have questions answered, and arrange unscheduled visits (using telehealth or in-person); Reports from remote imaging and labs should be received promptly for safety monitoring
  - **Task Log**: Including (1) names/affiliations of local HCPs performing trial-related tasks, (2) their roles and assigned tasks, (3) dates local HCPs are added to the log, and (4) locations where activities conducted..to be dated and signed by the investigator when created and updated, and available to FDA during inspections
  - **CRFs**: Should identify when and where data were collected and by whom

Differences in the EMA DCT Recommendations (1/2)

- No discussion of the role of the **HCP**.
- Discussion emphasizing the importance of **patient voice** and input in an "early and sustained manner" as well as including investigators and providers in design, development and implementation.
- **Burden** of DCT-related procedures must be weighted against the benefits for participants and PIs.
- Decentralized elements should be detailed in the **cover letter** for regulators.
- Use of additional service providers in DCTs bring additional considerations to ensure proper safety procedures. In additional, the **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.
- In general, the **consent process** should include a physical meeting of investigator and participant, but in some cases it can be justified to be done remotely. The consent should involve face-to-face communication which can be done via video in real-time.

Differences in the EMA DCT Recommendations (2/2)

- Discussion on strategies for PI to support safety review of **high-volume / sensor-derived data**.
- The participant should be given the **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.
- Extensive discussion on the need for **Investigator oversight** and that Investigator and Sponsor responsibilities/oversight are 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
  - Where service providers are being delegated a trial task but are being selected and contracted by the sponsor, the sponsor must ensure qualification and experience but the PI must be able to perform their own diligence to agree or not; the sponsor-PI contract should also document the arrangement with service providers

Agenda

- Why care?
- Guidance for all?
- Are we ready?
- What's left?

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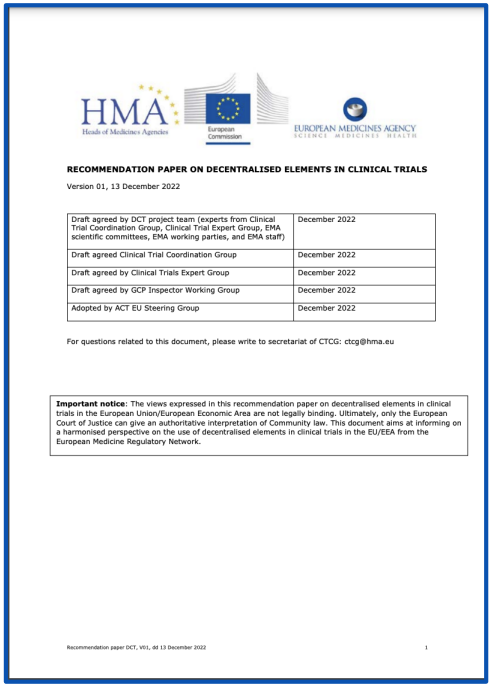
Clinical trials are global



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Heads of Medicines Agencies
European Commission
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

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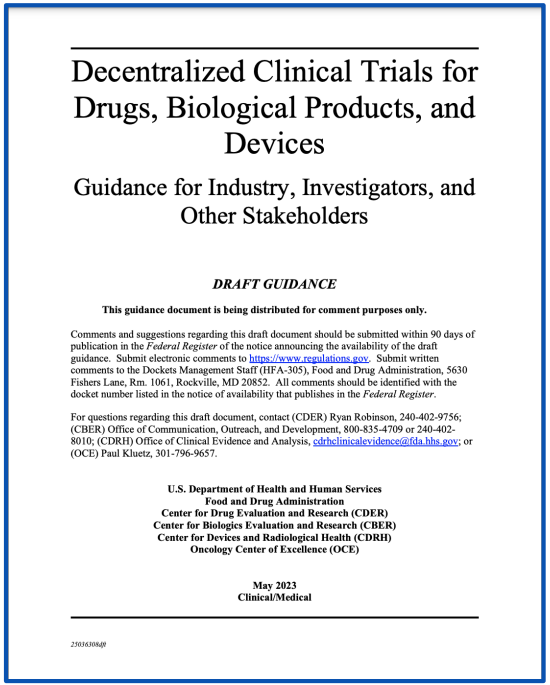
Draft agreed by GCP Inspector Working Group	December 2022
Adopted by ACT EU Steering Group	December 2022

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

Important notice: The views expressed in this recommendation paper on decentralised elements in clinical trials in the European Union/European Economic Area are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law. This document aims at informing on a harmonised perspective on the use of decentralised elements in clinical trials in the EU/EEA from the European Medicine Regulatory Network.

Recommendation paper DCT, V01, dd 13 December 2022 1



Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

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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

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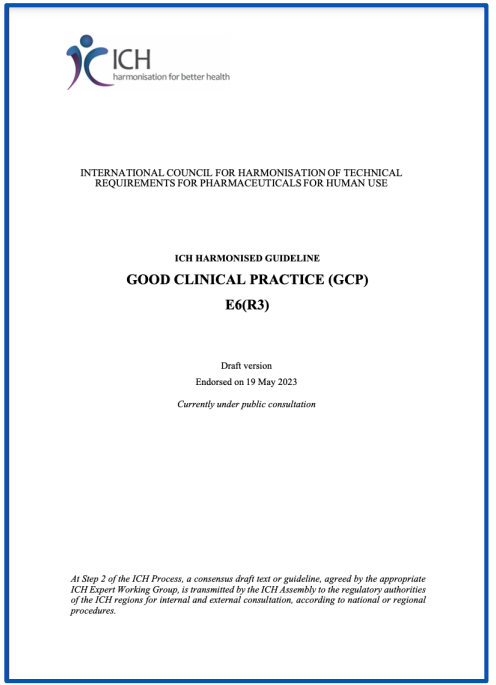

ICH
harmonisation for better health

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

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

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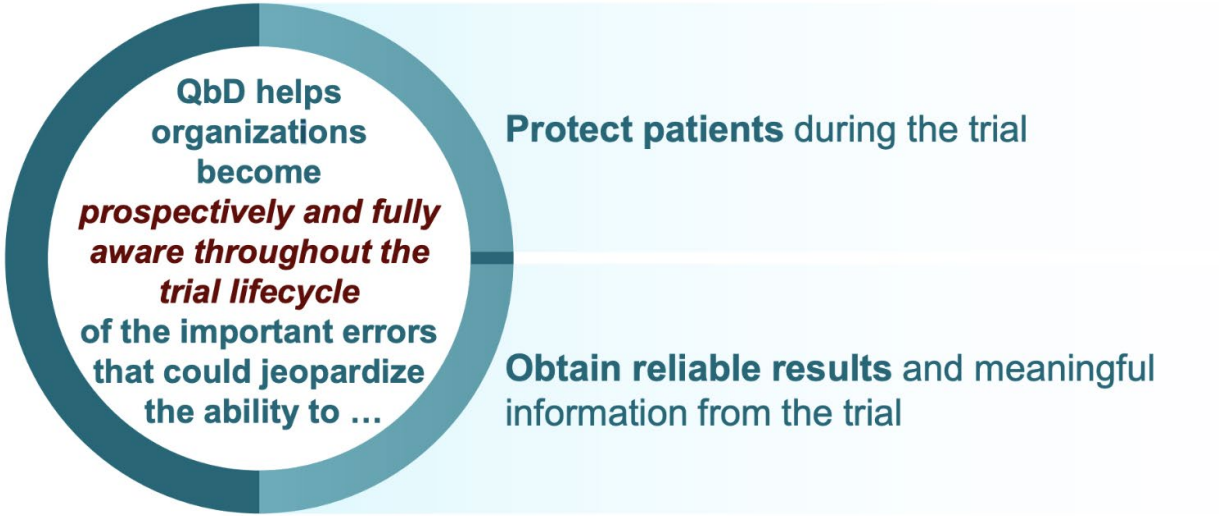
Quality by Design (ICH E8 section 3.1)

Optimize DCT elements for Patient Safety and Reliability of Results



https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-e8-r1-general-considerations-clinical-studies_en.pdf
https://ctti-clinicaltrials.org/wp-content/uploads/2021/08/CTTI_QbD_Toolkit_What_Is_QbD.pdf

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Key remaining items

- HCPs issues
  - First introduction in guidance
  - Task log
  - Need tools to facilitate adoption
- PI oversight
  - Need tools and framework
  - Many collaborations
    - ACRP
    - ACT@POC
    - ASCO
    - DTRA
    - Medable & MRCT

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HCP issues

Classification of physicians as HCPs versus sub-investigators

- If assessments are non endpoint or endpoints does that make a difference
- Is there a difference in overseeing HCPs performing standard-of-care tasks versus overseeing sub-investigators?
- How does it work when local providers and HCPs are the responsibility for the site PI but contracted with a sponsor in terms of FWA, engagement, and research?
- When it comes to payments for HCPs and study sites– there is a risk of “paying twice for services” that may only be done once, etc

Potential Tools for HCPs

- Roles and Responsibilities
- Training

PI Oversight

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The person designated as the Principal Investigator

- Needs to know what's going on
- Is responsible for patient safety and reliability of data

Oversight should be risk based based, proportionate and appropriate

- Critical to Quality Factors ICH E8R1/CTTI QbD recommendations

Factors that impact PI oversight

Degree of risk (low, medium, high)

- the participant
  - Indication, Population, Phase of development
- The data
  - How, where and by whom data are collected
- The IMP
- Study execution
- The DCT elements
  - Trust of data collecting sensors/ risk of HH in participants house
  - HCPs vs Sub-Is

Survey (CVS, Medable & MRCT)

Purpose

Determine what PI oversight and responsibility means in the new world of clinical trials and different emerging parties such as local providers, in the context of a decentralized clinical trial (DCT) for regulatory submission

Definition

For purposes of this survey, a DCT is one that requires one or more visits or assessments to be performed at a participant's home or within their local care community

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Readiness summary

- There are questions on oversight for all trials, traditional and DCT
- There are varying opinions/suggestions as DCT experience is still limited
- Data may be more directional in smaller sample size responses
- Trials themselves vary with IMP risk, decentralized approach, trial complexity, phase/severity of disease, therefore general guidance is necessary because of large degree of variability
- Trials are disparate in their deployment of different DCT elements possibly requiring a matrixed framework that considers each decentralized element and trial characteristics

Ethical Review of DCTs

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IRB/EC Considerations for DCT review

People
Remote data collection
Data Oversight

Scan to access recommendations

https://mrctcenter.org/resource/irb-ec-considerations-for-dct-review/

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Device Considerations

Equity: Consider	BYOD	Provisioned
• Equity issues when minimum device requirements are not met	✓	✓
• What the options are for participation if data plan is insufficient?	✓	
• Security and confidentiality in data transfers	✓	
Ensure Consent includes:		
• Costs and use of device and whether replacements devices are available (at what cost)	✓	✓
• Ensure Instructions and process are available if device lost, damaged, stolen	✓	✓
Consider disposition at end of study (keep or return)	✓	✓
Ensure appropriate instructions and training	✓	✓
Ensure access to helpdesk troubleshooting		✓

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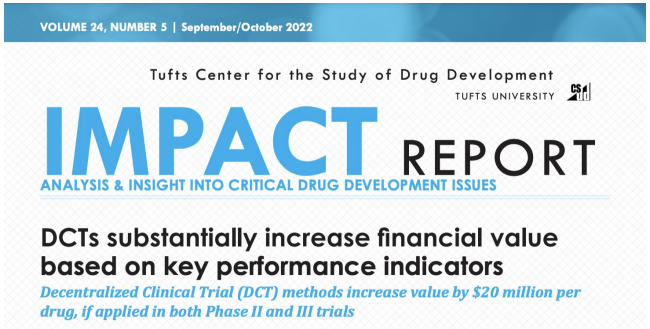
DCTs ROI & protocol performance



Scan to access

Application of DCT methods results in performance improvement in three factors studied

Factors impacted by DCTs

	Phase II		Phase III	
Performance indicators	**DCT**	**Non-DCT**	**DCT**	**Non-DCT**
Substantial protocol amendments	2.4	3.3	3.2	3.4
Screen failure rate	24.1%	31.5%	20.1%	29.9%
Phase duration (months)	27	30	28	31

Source: Tufts Center for the Study of Drug Development

- Tufts CSDD and Medable, Inc. data indicate that the application of DCT methods results in a reduction of 27% in substantial protocol amendment filings for Phase II trials and a reduction of 6% for Phase III trials.
- Screen failure rates are reduced, on average, by 7.4% for Phase II trials and by 9.8% for Phase III trials with DCT methods.
- Tufts CSDD benchmark data indicate an approximate 10% reduction in Phase II and Phase III trial phases with the application of DCT methods.

Assessing the Financial Value of Decentralized Clinical Trials: https://link.springer.com/article/10.1007/s43441-022-00454-5

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Agenda

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- Are we ready?
- What's left?

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Doing: A Checklist For Decentralized Clinical Trials

Trial Domain	Hard	Easy
Engagement (Patient, Clinician)		
Eligibility criteria confirmation		
Representative cohort		
Consent Comprehension Format		
Data Collection		
Quality assurance (Source documents)		
Safety/Pharmacovigilance		
Endpoint adjudication/validation		

Moving forward on remaining issues

- How do you engage people (direct to participant from the health system)?
- How do you cross state borders (federal vs state law) especially with interventional product supply?
- What is proper oversight for the HCP? What are the expectations for a Task Log?
- How do you *reliably and ethically* link data to DTP platforms?
  - Via patients
  - Via health care systems
  - Via other
- How do you promote diversity and inclusion?
- How do you ensure data quality?

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What's else? YOU!!

- Comment on guidance
  - FDA DCT draft guidance (Aug1)
  - ICH E6 R3 (end of October)
- Learning & Sharing
  - Research on Research
  - Tools development
  - Using tools and providing feedback
- IMPLEMENTATION!