



# **New Trends In Clinical Trial Designs: Decentralized Clinical Trials (DCTs)**

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# Learning Objectives

**Discuss**

- 1** FDA initiatives on trial modernization
- 2** Terminology and basic principles on DCTs
- 3** Regulatory requirements and DCTs

# Learning Objective: DCTs *(cont.)*



## **Discuss**

### **1. FDA initiatives on trial modernization**

# An Overview of the 21<sup>st</sup> Century Cures Act



- The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.
- The law builds on FDA's ongoing work to incorporate the perspectives of patients into the development of drugs, biological products, and devices in FDA's decision-making process.
- **Cures enhances FDA's ability to modernize clinical trial designs and clinical outcome assessments, which will speed the development and review of novel medical products, including medical countermeasures.**
- **Work Plan:**
  - The Cures Act authorized \$500 million over 9 years to help FDA cover the cost of implementing the law.
  - The final work plan, which includes the recommendations from FDA's Science Board, was delivered to Congress on June 9, 2017.

# Historical Perspective for DCTs: Guidances



- **Computerized Systems Used in Clinical Investigations (2007)**
  - Recommendations for the use of computerized systems in clinical investigations
- **E-Source Data in Clinical Investigations (2013)**
  - Data comes from multiple sources including patients, providers, devices, EHRs, etc.
- **Use of Electronic Informed Consent (2016)**
  - Informed consent can be obtained remotely via internet
- **Use of E-records and E-signatures in Clinical Investigations Under 21 CFR Part 11 (Draft, 2017)**
  - Outlines scope and application of part 11 requirements for clinical investigations of medical products
  - Electronic data transmission, audit trails from electronic devices
- **Digital Health Technologies Efforts**
  - Use of mobile devices, biosensors, etc. in clinical investigations

**... Now Decentralized Clinical Trials**

# Public News: Modernization of Clinical Trials



- **FDA Presents Approach to Real-World Evidence in Clinical Trials.**

- *“It’s a recognition that new approaches and technologies can help expand the sources of evidence that we can use to make more reliable treatment decisions. And it’s a recognition that this evidence base can continue to build and improve throughout the therapeutic life of an FDA approved drug or medical device.”*
- *He described so-called “pragmatic and hybrid clinical trials,” which includes **decentralized trials** performed at the point of care. These, he said, “can help clinical trials become more agile and efficient by reducing administrative burdens on sponsors and those conducting trials and can allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that’s being collected.”*

**January 29, 2019 – BioSpace:**

<https://www.biospace.com/article/fda-s-gottlieb-presents-approach-to-real-world-evidence-in-clinical-trials/>

- **FDA Statement on New Strategies to Modernize Clinical Trials to Advance Precision Medicine, Patient Protections and more Efficient Product Development.**

- *“The agency has worked closely with stakeholders, including the Clinical Trial Transformation Initiative, to identify innovative trial designs, evaluate the role of **decentralized clinical trials** and mobile technologies, and help validate novel endpoints that can enable trials to generate reliable evidence needed to assess product safety and efficacy more efficiently.”*

**March 14, 2019 – FDA Pres Announcements:**

<https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-strategies-modernize-clinical-trials-advance>

# Public News: Modernization of Clinical Trials *(cont.)*



- **FDA Calls for Greater Adoption of New Clinical Trial Tools.**

- *“The Food and Drug Administration is stepping up its efforts to encourage wider adoption of new clinical trial methods, **issuing new guidance documents** Thursday intended to help drugmakers and clinical researchers design more efficient and less costly studies.”*
- *“Techniques like **decentralized clinical testing** or master protocol designs hold significant potential, but haven't been as broadly used as the regulator would like.”*

March 15, 2019 - Pharma Dive:

<https://www.biopharmadive.com/news/fdas-gottlieb-calls-for-greater-adoption-of-new-clinical-trial-tools/550598/>

- **FDA Calls on Industry to Modernize Approach to Clinical Trials.**

March 18, 2019 – Global Genes:

<https://globalgenes.org/2019/03/18/gottlieb-calls-on-industry-to-modernize-approach-to-clinical-trials/>

- **FDA Talks About Modernizing Clinical Trials.**

March 21, 2019 – Medium:

<https://medium.com/@TheRealDanSfera/fdas-gottlieb-talks-about-modernizing-clinical-trials-e27d6f339d97>

- **Clinical Trials Transformation Initiative. CTTI Recommendations: Decentralized Clinical Trials**

September 2018 – CTTI:

[https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/dct\\_recommendations\\_final.pdf](https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/dct_recommendations_final.pdf)

# Learning Objective: DCTs *(cont.)*

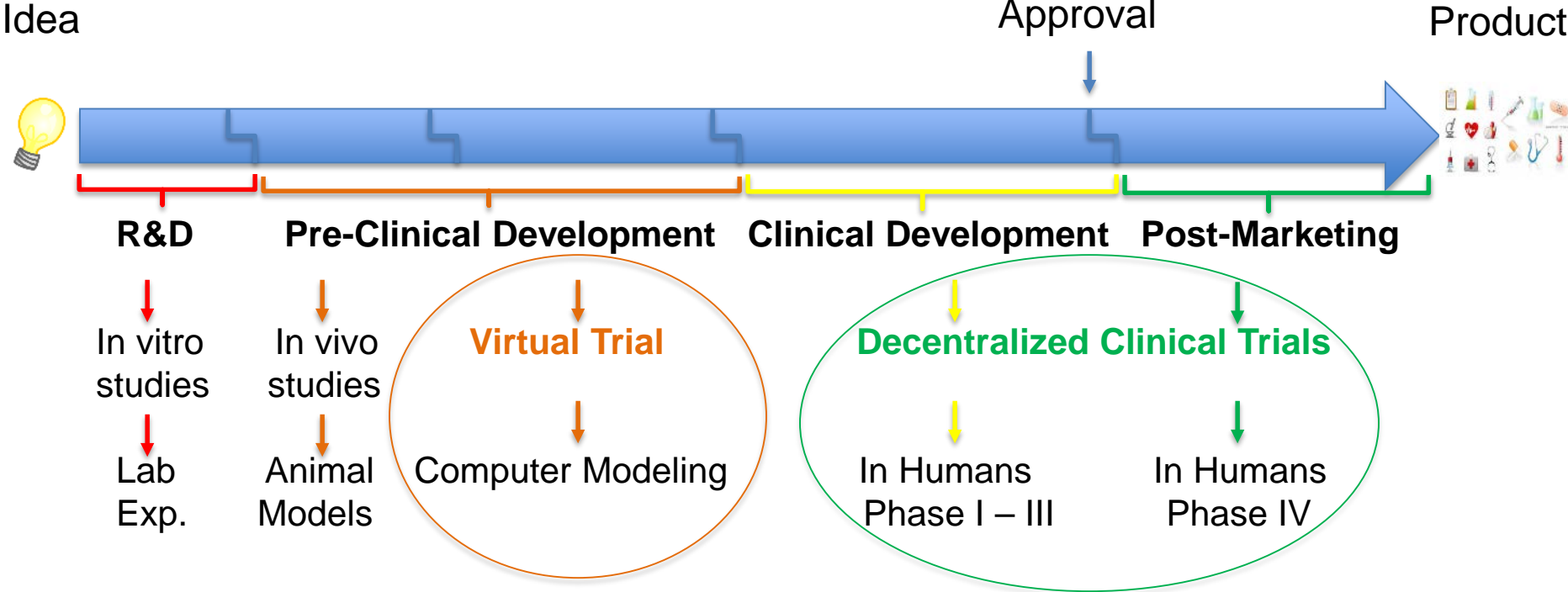


**Discuss**

**2. Terminology and basic principles on DCTs**



# Life Cycle of a Medical Product



# Decentralized Clinical Trials (DCTs)

## Background

- **Advances in electronic communication, data transmission, digital technology and biosensor development present new opportunities to exchange information with locations remote from the investigator such as patients' homes.**
- **Trials in which some or all study-related procedures and data acquisition take place at locations remote from the investigator (i.e., spectrum: CCTs → Hybrid Models → DCTs).**
- **Trials can be designed as an integration of the study subject's existing healthcare system, maximizing convenience for study subjects and taking advantage of services and data sources already in place including:**
  - **The study subjects themselves through the use of telecommunication, videoconferences, mobile or internet-based tools for patient reporting, mobile technology tools and biosensors.**
  - **Local healthcare providers, pharmacies, clinics, home based healthcare services, regional hospitals.**



# DCTs: Thoughts on Basic Principles

- **The personnel**
  - Investigator means an individual who actually conducts a clinical investigation (i.e. , under whose immediate direction the drug is administered to a subject). The investigator is the responsible leader of the team if the team exists.
  - Sub-investigator includes any other individual member of the team who is qualified to carry out the investigator duties
  - Local health care providers (local clinics, local physicians, nurses, physical therapists, phlebotomists)
  - Ancillary medical services (radiology, laboratories)
  - Support services (IT/Digital Health Technologies, transport, administrative)
- **The site**
  - The address of the study site is the address of the investigator. This is the place where the investigator conducts, oversees and coordinates trial activities.
- **The tools**
  - Digital Health Technologies (DHTs), telemedicine, and other evolving technologies for communication via video and/or audio.
  - Remote data acquisition, transfer, management and storage.
- **Study participant's safety**
  - Same standards as for traditional trials.
  - Acquisition of continuous or more frequent clinical data may lead to new safety data.
  - Ensure access to appropriate and prompt care for adverse events.
  - Ensure prompt capture of safety data from study participants and health care providers.
  - Subjects need to be informed how to contact their healthcare provider or emergency personnel for any concerning symptoms.

# DCTs: Opportunities - Advantages



- **Continuous or more frequent collection of clinical data.**
  - Potential data alignment with SOC guidelines.
- **Potential to reach a broader population– cohorts.**
  - Access to subjects with limited mobility.
  - Broaden subject access and demographics.
    - But need to be attentive to technology creating barriers for certain subjects.
  - Reduction of geographic barriers.
  - Rapid recruitment through increased access.
- **May align with clinical practice environment.**
  - Use of DHTs, telemedicine.
  - Use of local health care providers, laboratories, imaging places (local environment).
- **Potential for long term follow-up if burden reduces.**
- **Reduction of burden on study subjects, caregivers and clinical sites.**
- **May lead to faster, less expensive trials.**

# Safety Monitoring in DCTs



- **Standards for safety monitoring and reporting adverse events (AEs) are the same in traditional and decentralized trials.**
- **Safety monitoring plan is protocol specific.**
- **Escalation plan includes instructions for study subjects, DCT personnel, local health care providers, and 3rd party vendors.**
- **Study subjects may not have regular in-person contact with the investigator/DCT personnel.**
  - DCT personnel are available to study subjects through telemedicine: schedule visits, get advice, report AEs.
  - Investigator must ensure that there is appropriate and timely care for medical emergencies and follow-ups.
  - Study subjects must be informed about how to address AEs and where to seek medical assistance.
  - Investigator collects information from local health care providers when used by study subjects and report AEs to sponsor.
- **In general, it is recommended to have regular (remote) visits in DCTs as done in traditional trials.**
  - Use of DHTs to communicate with DCT personnel.
  - Access to local health care providers, clinical laboratory and imaging facility services.
- **Distinction between two remote activities:**
  - Continuous data acquisition.
  - Data monitoring to provide timely medical response.



# Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial

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- **First example of an entirely web-based trial under IND (example of a full DCT).**
- 5157 patient registered, 456 signed consent, 188 in placebo run in, 18 randomized to treatment.
- Electronic informed consent.
- Randomized to tolterodine 4mg daily x 12 weeks vs placebo.
- Electronic diaries.
- Decreased micturition/24 hours: tolterodine - 2.4 placebo - 0.8.
- Treatment difference (95% CI): – 1.6 (– 3.9, 0.6).

# Learning Objective: DCTs *(cont.)*



**Discuss**

## **3. Regulatory requirements and DCTs**

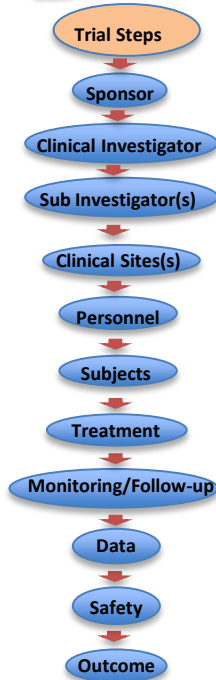
# Comparing Clinical Trial Models



**Subject's Safety & Confidentiality**

**Clinical Data Quality & Integrity**

**SAME Regulatory Requirements (CFR) for TCTs and DCTs**



Traditional Clinical Trial (TCT)	Decentralized Clinical Trial (DCT)
Responsible for TCT	Responsible for DCT
Manages central site(s)	Manages remote locations
Work in central site(s)	Work in remote locations
Centralized locations	Remote locations
Assigned to central site(s)	Assigned to remote locations
Recruited at central site(s)	Recruited remotely
Administered at central site(s)	Administered remotely
Coordinated at central site(s)	Coordinated remotely
Site(s): Capture/transmission	Remote: Capture/transmission
Monitoring: Central site(s)	Monitoring: Remotely
Data quality and integrity	Data quality and integrity





# DCTs and Regulations



- **Current regulations focus on the investigator and the clinical trial site.**
  - **21 CFR, Part 312.53.a** – Selection of Investigator.
  - **21 CFR, Part 312.53.c** – Obtaining information from the investigator (Form FDA-1572).
    - i – Name and address of the investigator (a remote health care provider).
    - iii – Name and address of research facility where the clinical investigation will be conducted (study subjects' homes).
    - iv – Name and address and address of any clinical laboratory facilities to be used in the study (all remote labs, imaging services).
    - vi.d – Investigator will personally conduct or supervise the described investigation (remote settings).
  - **21 CFR, Part 312.53.g.viii** – Name of sub-investigators (all remote health care providers participating in a trial).
  - **21 CFR, Part 312.64.b** – Safety reports by investigator (AE reporting by remote health care providers).

Other items:

  - **21 CFR, Part 11, Subparts B, C** – Electronic records – compliance of e-platforms (DHT efforts).
  - **21 CFR, Part 50, Subpart B** – Obtaining informed consent (addressed in e-Informed Consent and DHT efforts).
  - **21 CFR, Part 312.68** – Inspections of investigator's records and reports (source documents using DHTs remotely).
- **DCTs do not use traditional clinical trial sites.**
  - FDA's goal is to help sponsors and investigators meet their regulatory responsibilities when conducting DCTs.
    - Appropriate oversight of:
      - Remote locations (local clinics, patients' homes).
      - Local health care providers (local physicians, nurses, pharmacists).
      - Local health care facilities (laboratories, pharmacies, imaging services).

# Key Considerations to Conduct DCTs in Multiple Jurisdictions *(cont.)*



## Regulations:

- **For clinical research:** Code of Federal Regulations
- **For clinical care:** Jurisdictional laws (e.g., state and country laws and regulations)

# Key Considerations to Conduct DCTs in Multiple Jurisdictions



- The **investigator** may be licensed in one jurisdiction and...
  1. Conducts study visits via telemedicine with study subjects in other jurisdictions.
  2. Administers IMPs to study subjects remotely (e.g., located in other states).
  3. Complies with jurisdictional laws and regulations.
- The **sponsor** checks jurisdictional licensing laws for the following:
  1. To see if investigators or subinvestigators acting as medical providers in DCTs need to be licensed in jurisdictions where study subjects are located.
  2. To see if providers licensed in those jurisdictions should be engaged.

# Key Considerations to Conduct DCTs in Multiple Jurisdictions *(cont.)*



## Regulatory requirements to mail drugs across different jurisdictions:

- **For investigational MPs:**
  - 21 CFR §312.53(a): It requires sponsors to select only those investigators who are qualified by training and experience as appropriate experts to investigate IMPs.
  - 21 CFR §312.61: It refers to the control of the investigational drug under the investigator/subinvestigator – IMPs to be administered only to study subjects.
  - 21 CFR §312.62: It refers to investigator recordkeeping and record retention. (a) Disposition of drug. (b) Case histories. (c) Record retention.
- **For licensed MPs:**
  - Jurisdictional laws (state and country laws)

# Key Considerations to Conduct DCTs in Multiple Jurisdictions *(cont.)*



**1** Clinical trial design and technology

**2** Logistics – resources and implementation

**3** Regulatory, policy, law – compliance - jurisdictions

**4** Finances – means to do it and affordability

# Challenge Question



**True or False:**

- 1. DCTs are virtual trials done remotely.**
- 2. DCTs are randomized trials done remotely.**
- 3. DCTs follow a new set of FDA regulations.**
- 4. All of the above statements are correct.**



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