New Era of Clinical Trials in a Conservative Industry: A Hybrid Approach to Decentralized Clinical Trials (DCT)

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Perspectives

- Industry Professional
- Consumer
- Quality Assurance Leader
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Decentralized Clinical Trials (DCTs)

DCT = Refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites.

In fully decentralized clinical trials, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants.

In **hybrid DCTs**, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes.

From: - Reference #1 - FDA DRAFT Guidance Document (May 2023): Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Background and Why

- Advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (i.e., telehealth) allow for fewer in-person visits to clinical trial sites.
  - Digital health technologies (DHTs), for example, have expanded the types of trial-related data that can be obtained remotely from trial participants

- DCTs have the potential to expand access to more diverse patient populations and improve trial efficiencies.
  - By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites.
  - This may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.

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Perspectives #1 & #2

Industry Professionals & Consumers

Industry Perspective on DCTs

- Decentralization has been happening for a while; and technological, communications, and authentication advancements are pushing us to move along with the tide.
- FDA and other regulatory bodies are embracing DCT, as evidenced by the numerous recent guidances that refer to DCT, tele-health, digital medicine, and real-world data.

Draft Guidance: "…Include, as appropriate, the use of local health care facilities, local HCPs, and local clinical laboratory facilities; visits to trial participants' homes; and direct distribution of the IP to trial participants at their locations."

- We, as an industry, need to embrace the trend; however, we must understand BOTH how to utilize DCT and technology to reach out to intended patients and participants – AND how to be efficient, compliant, and ethical.

From: - Reference #1 - FDA DRAFT Guidance Document (May 2023): Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Industry Perspective on DCTs – Link to Diversity Initiatives

"Individuals from [certain] populations are frequently underrepresented in biomedical research despite having a disproportionate disease burden for certain diseases ... Adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved, and may potentially identify effects on safety or efficacy outcomes that may be associated with, or occur more frequently within these populations."

From: - Reference #2 - FDA DRAFT Guidance Document (April 2022): Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

Industry Perspective on DCTs – Link to Diversity Initiatives

It is important that trial participants represent the populations most likely to use the potential medical product. However, often, the characteristics of the clinical research participants do not match the characteristics of the epidemiological populations or even the general population.

Demographic Characteristics:

- Sex race, ethnicity, age, location of residency

Non-Demographic Characteristics:

- Organ dysfunction, comorbid conditions & disabilities, those at weight range extremes, and populations with diseases or conditions with low prevalence

From Reference #3: - November 2020 FDA Statement: FDA Offers Guidance to Enhance Diversity in Clinical Trials, Encourage Inclusivity in Medical Product Development

Industry Perspective on DCTs – Link to Diversity Initiatives

In November 2020 FDA issued a new Guidance for Industry that clearly links DCT to the FDA's diversity initiatives.

"Make Trial Participation Less Burdensome for Participants

…consider whether flexibility in visit windows is possible and whether electronic communication (e.g., telephone/mobile telephone, secured electronic mail, social media platforms) or digital health technology tools can be used to replace site visits and provide investigators with adequate real-time data. Consider the use of mobile medical professionals, such as nurses and phlebotomists, to visit participants at their locations instead of requiring participants to visit distant clinical trial sites."

From Reference #4: - November 2020 FDA Guidance Document: Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs

Why is Decentralization & Diversity Important to Consumers?

- As consumers, we want to know the drugs and devices that make it to Market have been tested fully in the populations that will be using the product.
- If we have elderly relatives, young children, or loved ones who suffer from co-morbid conditions and/or use concomitant medications, we want to be able to trust that the formulations and dosages of prescribed and OTC medications have been thoroughly tested and proven to be safe and effective in people with similar characteristics.

Decentralization is needed to reach a broader and more diverse population of research participants.

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Quality & Compliance

Taking a Quality Approach to DCT & Diversity Planning

Taking a quality approach, means:

Identifying there is a problem	"Medical product development programs should consider the clinical and demographic factors that impact the generalizability of study results with respect to the patient population that will use the medical product once it is approved."
Investigating, determining scope and impact	"…sufficient Pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data from a diverse population is strongly encouraged to inform analyses of drug exposure and response." "When there are data that indicate that the medical product may perform differentially across the population…in some cases, increased…enrollment of certain populations may be needed…"
Determining root cause	The sponsor should evaluate enrollment metrics and feasibility to identify barriers that exist to diverse enrollment and continued participation.
Determining and Implementing appropriate corrective and preventive actions	"[FDA] recommends that sponsors develop *a plan that outlines the operational measures that will be implemented to ensure diverse clinical trial participation* to improve the generation of evidence regarding safety and effectiveness across the entire program…"
Performing Effectiveness Checks to determine if CAPA was effective	KPIs and metrics should be collected and assessed on a continuing basis, during study enrollment, to confirm effectiveness of plan or to determine the need for improvement.

From: - Reference #2 - FDA DRAFT Guidance Document (April 2022): Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

DCT Challenges to Quality

Although there are many benefits to DCT, there are some major potential impacts to quality and compliance

- To facilitate DCT, there has to be less standardization across sites and documentation to allow for established processes, systems, and practices.
- Utilizing multiple vendors and technologies creates a complicated delegation and oversight model.
- Less standardization and complicated delegation and oversight models often result in lower quality (more errors, later detection, lack of oversight and accountability)
- New technology isn't always the answer
  - Could cause exclusion of certain participants or research centers or create start-up delays/bottlenecks
  - Complicates the monitoring paradigm
- Question: How do you control things that are outside of your control?
  - Need processes, procedures, and systems that are flexible enough to facilitate differences when differences are warranted
  - Need a work force that can see the big picture

Need to get back to basics!

Back to Basics – Assuring Regulatory Compliance

FDA's regulatory **requirements for investigations of medical products are the same for DCTs and traditional site-based clinical trials**.

- Section 360(a) of the Food and Drug Omnibus Reform Act (FDORA) directs FDA to "issue or revise draft guidance that includes recommendations ***to clarify and advance the use of decentralized clinical studies to support the development of drugs and devices***," not later than December 29, 2023.
- The FDA DRAFT Guidance Document (May 2023): Decentralized Clinical Trials for Drugs, Biological Products, and Devicesprovides recommendations related to FDA's requirements for investigations of medical products when applied to DCTs and fulfills the requirement set forth in section 3606(a)(1) of FDORA.
- The content described in section 3606(b) of FDORA is further addressed through this guidance's reference to the draft guidance for industry, investigators, and other stakeholders entitled Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (December 2021)[5]

From Reference #5 - FDA Final Guidance Document (Dec 2023): Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Back to Basics – Assuring Regulatory Compliance

In a nutshell…
…If you have the regulatory responsibility for it, you must either DO it or DELEGATE it (qualify, inform, and oversee)

From Reference #6 – ICH E6(R2) (March 2018): Integrated Addendum to ICH E6(R1)

Getting Back to Basics

What does the DCT workforce need to master and embrace to effectively implement DCT while maintaining the desired level of quality?

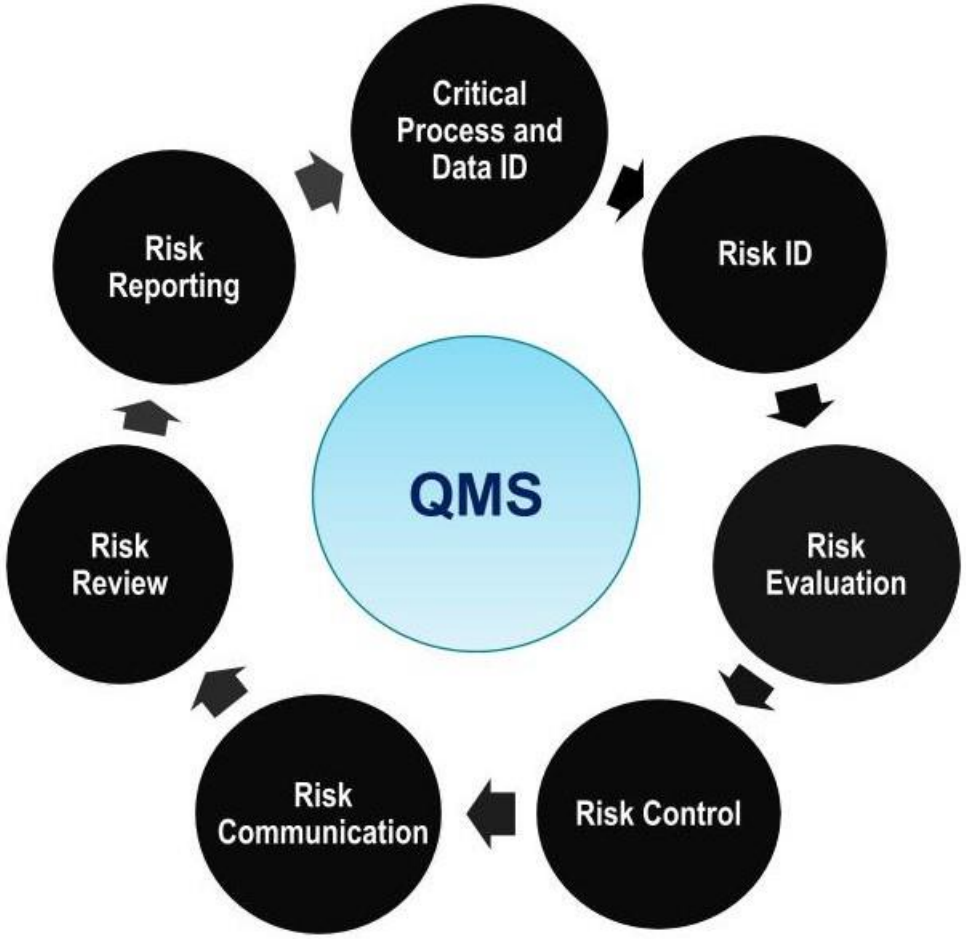
- Understanding of organization and content of ICH E8[7] and ICH E6 (R2, headed toward R3)
- Understanding of FDA requirements for sponsors, investigators, and IRBs/ECs involved in the development of drugs and devices, and how these requirements line up with GCP
- Ability to follow a data trail
- Understanding of good documentation practices and how it applies to paper, electronic, and hybrid source documentation systems
- Understanding of basic concepts of risk management, risk-based monitoring, and risk-based quality management
- Access to clear, detailed, but flexible SOPs, protocols, site instructions, and study plans that provide an adequate and efficient roadmap

Getting Back to Basics

Ensure CONTROL when tasks/documentation are outside of normal standardization and controls

- Assure quality and consistency of critical study activities performed remotely
- Maintain control, accountability, proper storage conditions, and Participant privacy when delivering IP remotely
- For inspectional purposes, ensure there is a physical location where all clinical trial-related records for participants under the investigator's care are accessible and where trial personnel can be interviewed
- Manage challenges with Participant engagement during remote assessments, as well as compliance with the protocol and GCP
- Provide conceptual training and tactical training to core and peripheral study team members

Back to Basics – Quality Risk Management



From Reference #6 – ICH E6(R2) (March 2018): Integrated Addendum to ICH E6(R1)

- Map data flow from collection, to QC, to reporting, to monitoring/verification
- ID critical data and data interactions
- Determine risks with activities, involved parties, processes, documentation practices, direct access to data
- Evaluate risks and develop plans for operationalizing activities and managing & monitoring risks
- Ensure appropriate delegation and oversight
- Document site-specific and/or vendor-specific monitoring requirements, with quality tolerance limits and thresholds for action
- Review and update plans periodically and as-needed

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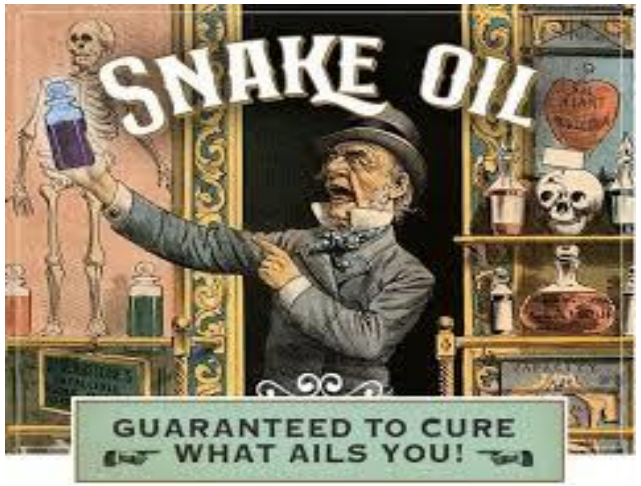
Perspective #4

Ethical & Human Research Participant Protection (HRPP)

HRPP Paradigm Shift

Focus has changed from “protection from” to “access to,” but underlying ethical principles are still applicable, as specified in the following standards.

- Nuremberg Code[8] (1947)
- Declaration of Helsinki[9] (1964)(2013)
- Belmont Report[10] (1979)
- ICH E6[6]
- IC E8[7]




The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

Primary Goal of Ethical Standards – Protect the Participants

Declaration of Helsinki (2013)
General Principle #8

"While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."

ICH E6
General Principle #2.3

"The rights, safety, and well-being of trial subjects are the most important considerations and should prevail over interests of science and society."

ICH E8
General Principle #2.1

"Important principles of ethical conduct of clinical studies and the protection of participants, including special populations, have their origins in the Declaration of Helsinki and should be observed in the conduct of all human clinical investigations. These principles are stated in other ICH guidances for industry, in particular, E6(R2) Good Clinical Practice…As further described in the ICH E6(R2) guidance, the investigator and sponsor have responsibilities for the protection of study participants together with the Institutional Review Board/Independent Ethics Committee.."

Belmont Report – Three Foundational Ethical Principles

- Respect for Persons
  - Autonomous vs Vulnerable
  - Fully Informed Consent and Voluntary Participation
- Beneficence
  - Potential benefits outweigh risks
  - Risks are minimized
  - Non-malfeasance
- Justice
  - Fairness
  - Reciprocity
  - The burden and benefit are proportionally distributed

From: - Reference #10 - The Belmont Report (1979): Ethical Principles and Guidelines for the Protection of Human Subjects of Research

Primary Goal of Ethical Standards – Principle of Justice

Application Requirement #3

"…the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects."

"Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research.

Primary Goal of Ethical Standards – Principle of Justice

Application Requirement #3

"Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Back to Basics: Ethical Standards – Don’t Repeat Mistakes of the Past

- Injustice – Heavier Burden
- Lack of Transparency – Mistrust of Clinical Research
- Therapeutic Misconceptions
- Undue Influence

Thanks for your attention!

Q&A

References

#1 - FDA DRAFT Guidance Document (May 2023): Decentralized Clinical Trials for Drugs, Biological Products, and Devices https://www.fda.gov/media/167696/download

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#3 - FDA Statement (Nov 2020): FDA Offers Guidance to Enhance Diversity in Clinical Trials, Encourage Inclusivity in Medical Product Development https://www.fda.gov/news-events/press-announcements/fda-offers-guidance-enhance-diversity-clinical-trials-encourage-inclusivity-medical-product

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References

#7 – FDA Final Guidance Document (Apr 2022): ICH E8(R1) General Considerations for Clinical Studies https://www.fda.gov/media/157560/download

#8 – Nuremberg Code (1947): Directives for Human Experimentation https://ori.hhs.gov/content/chapter-3-The-Protection-of-Human-Subjects-nuremberg-code-directives-human-experimentation

#9 – Declaration of Helsinki (1964): Ethical Principles for Medical Research Involving Human Subjects https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/doh-jun1964/; (2013) https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

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