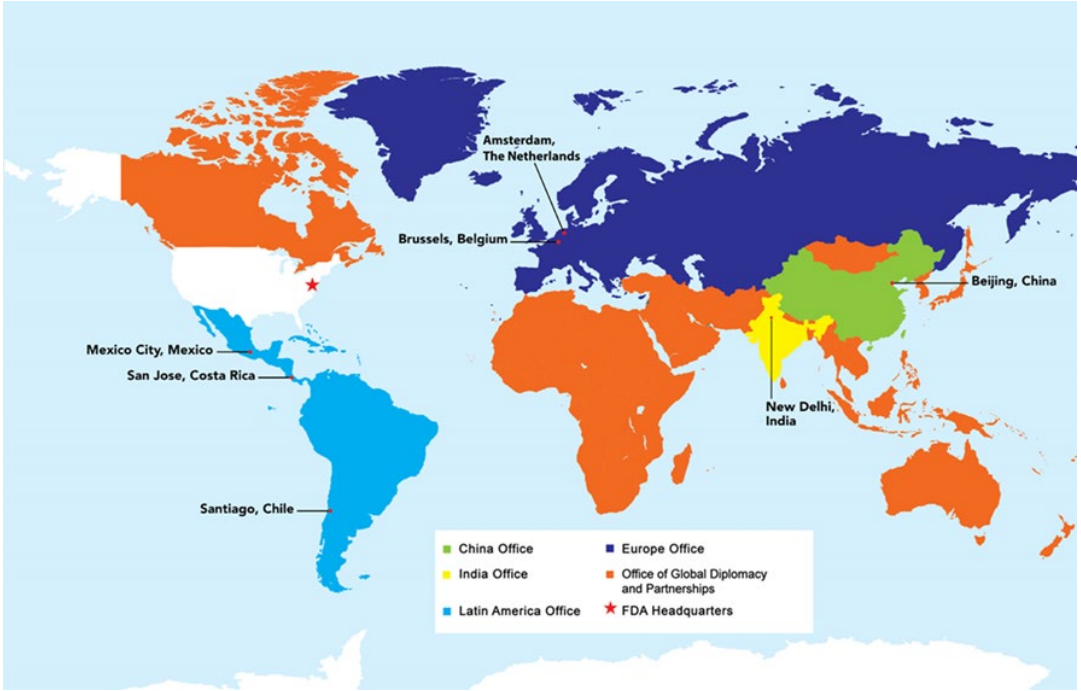
FDA and the Clinical Trial Infrastructure

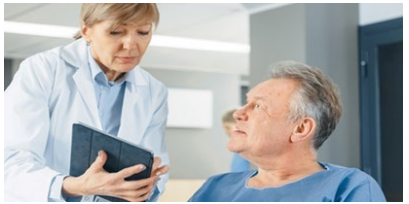
Mark Abdoo
FDA Associate Commissioner for Global Policy and Strategy

ISCR 16th Annual Conference, February 24, 2023

Office of Global Policy and Strategy



FDA and Clinical Trials



Clinical trials are conducted for many reasons:

- to determine whether a new drug or device is safe and effective for people to use.
- to study different ways to use current, approved treatments so that they will be more effective, easier to use, or decrease certain side effects.
- to learn how to safely use a treatment in a population for which the treatment was not previously tested, such as children.

FDA doesn't conduct the trials – we oversee them.

The Challenge

The COVID-19 pandemic demonstrated that the U.S. clinical trial infrastructure is not prepared for research needs that arise in the event of public health emergencies.

- 5% of 2,000 registered trials were randomized/adequately powered*
- Researchers implemented their own research protocols and captured and stored their own data.
- Resulted in relatively small, often inconclusive studies.
- This delayed the availability of vaccines, therapeutics and diagnostics and impeded the tracking of outbreaks.

**Nature Reviews Drug Discovery, K. Bugin and J. Woodcock*

UK's Recovery Trial

- Randomized, multi-arm master protocol: six treatments evaluated in a head-to-head comparison with standard of care as the control arm
- 7,586 patients enrolled across 172 sites within 1 month of protocol approval
- Within 3 months sufficient data to determine that dexamethasone effective in reducing mortality, while hydroxychlorquine was not.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Clinical Challenges Impacting Drug Development

- Trials have become more costly & complex to administer, which can make drug development more risky, uncertain, and time consuming.
- Overly complex trials can also deter enrollment & delay completion studies so long that findings aren't relevant for patient care.
- Adding to complexity is "endpoint creep."
- Phase II/Phase III protocols had 263 procedures on average per patient, supporting approximately 20 endpoints.*

**January/February Tufts CSDD Impact Report, 2021*

Unnecessary Trial Complexity Impedes Evidence Generation

"You start out with a beautiful green tree that should be admired, and then everybody in the family wants to put an ornament on it... and no one will take grandma's ornament off the tree. So you end up with a protocol that is impossible to do and is very distracted from answering the question you originally had."

- Dr. Robert Califf, Mind the Gap seminar, "Innovative Approaches to Clinical Trials"

FDA Actions

Encouraging pioneering advances in clinical trial design

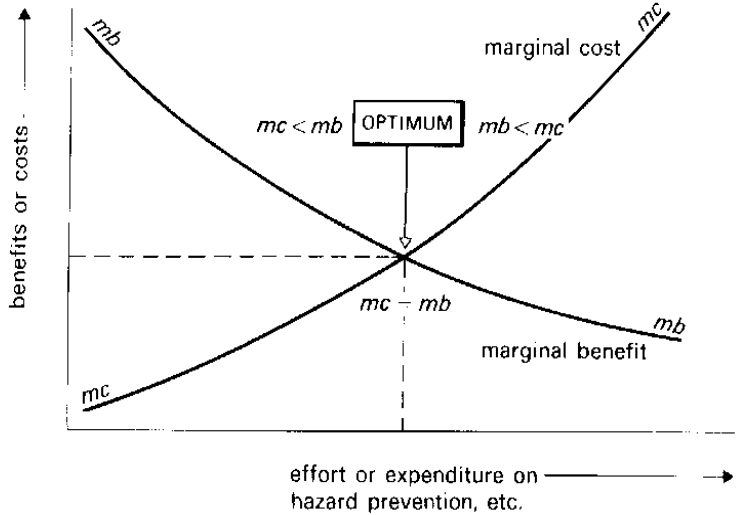
- Master Clinical Trial Protocols
- Seamless trials
- Decentralized trials
- Real World Evidence/Real World Data

Partnering with the Clinical Trials Transformation Initiative

Practical Considerations

Simply advocating the “highest level” of quality has little practical meaning in itself.

The cost associated with incremental improvements in quality becomes ever higher as perfection is approached and becomes disproportionate to any additional benefit achieved.



Re-Framing Quality

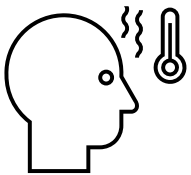
- “Quality” is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients)

CTTI: Recommendations for Quality by Design

Case Study Example

Cardiovascular Major Morbidity Outcomes Trials

- Critical-to-quality: strategies to ensure the survival status of all trial participants is captured
- Not critical-to-quality: source verifying participants' temperature readings obtained as a part of vital sign assessments at routine study visits



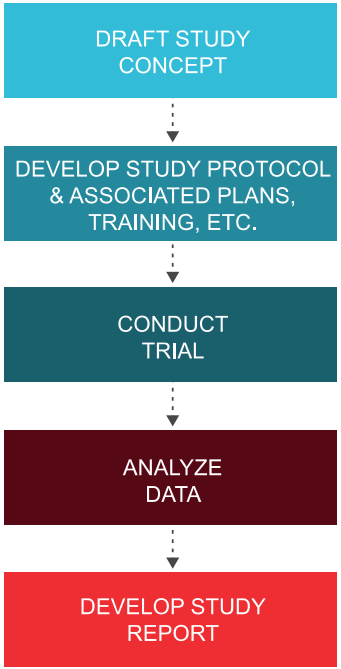
QbD Concepts in ICH E8

https://www.fda.gov/media/157560/download

ICH E8(R1) Design Considerations

- Whether the objectives are clearly articulated
- Whether the study is designed to meet the research questions it poses
- Whether these questions are meaningful to patients
- Whether the study hypotheses are specific and scientifically valid

QbD Approach to Study Design



Engage all stakeholders to…

- **Identify critical to quality aspects** of trial design and potential challenges
- **Tailor design** to avoid errors that could undermine evaluability or safety
- **Streamline** trial where feasible
- **Verify** proposed design consistent with scientific question
- **Highlight and evaluate** remaining risks

- Operationally feasible trial design that addresses questions relevant to stakeholders
- Efficient, focused trial oversight plans

Resources to Support QbD Implementation

- ….those interviewed by CTTI said they struggle to translate principles to practice.

Tools are needed!

CTTI QbD Toolkit

LEARN ABOUT QBD

HOME - Toolkit - QBD (QUALITY BY DESIGN) TOOLKIT - Learn About QbD

This section of the Toolkit provides an introduction to QbD through videos, downloadable presentations, and peer-reviewed articles. Learn about QbD and why it matters in clinical trials. Leverage these tools to teach others in your organization about QbD in order to secure their interest and support.

CTTI'S QBD RECOMMENDATIONS

The CTTI QbD project has produced recommendations on the use and implementation of QbD.

QBD Toolkit

Learn About QBD

Teach Others About QBD

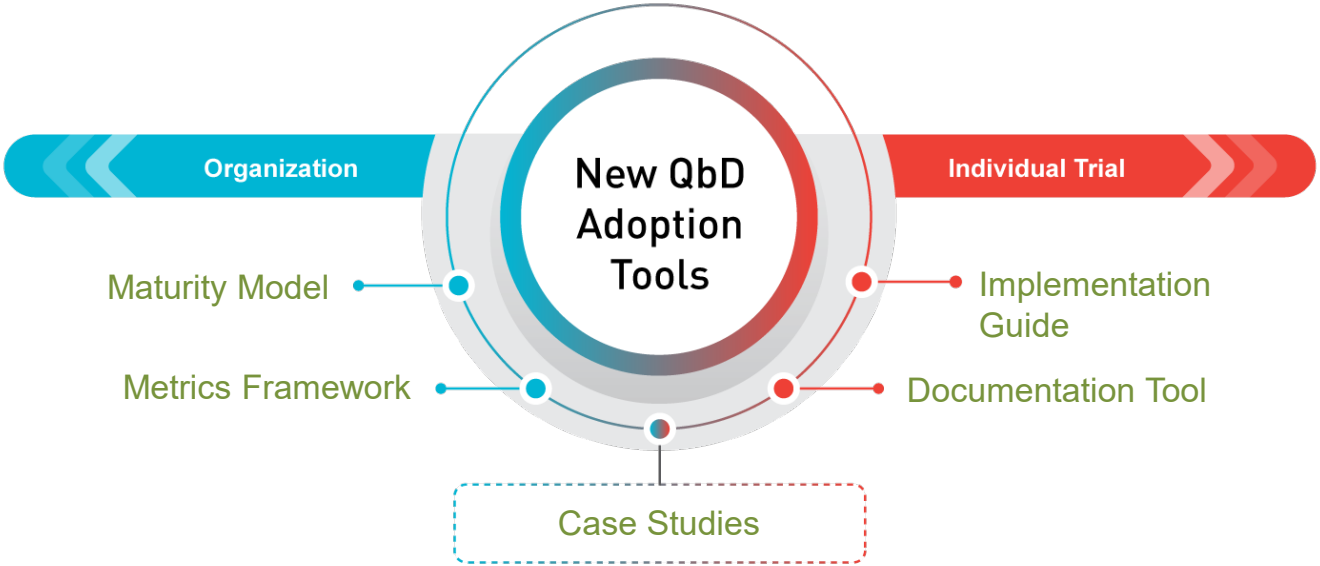
Adopt QBD

RESOURCES

- Principles Document (pdf)
- CTTI QbD Recommendations (pdf)
- Key Stakeholders (pdf)
- Maturity Model (doc)
- Metrics Framework (pdf)

Contact us for questions or comments on the QbD Toolkit

http://www.ctti-clinicaltrials.org/toolkit/QbD

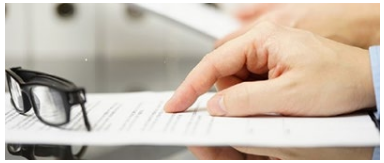


CTTI's Existing QbD Tools

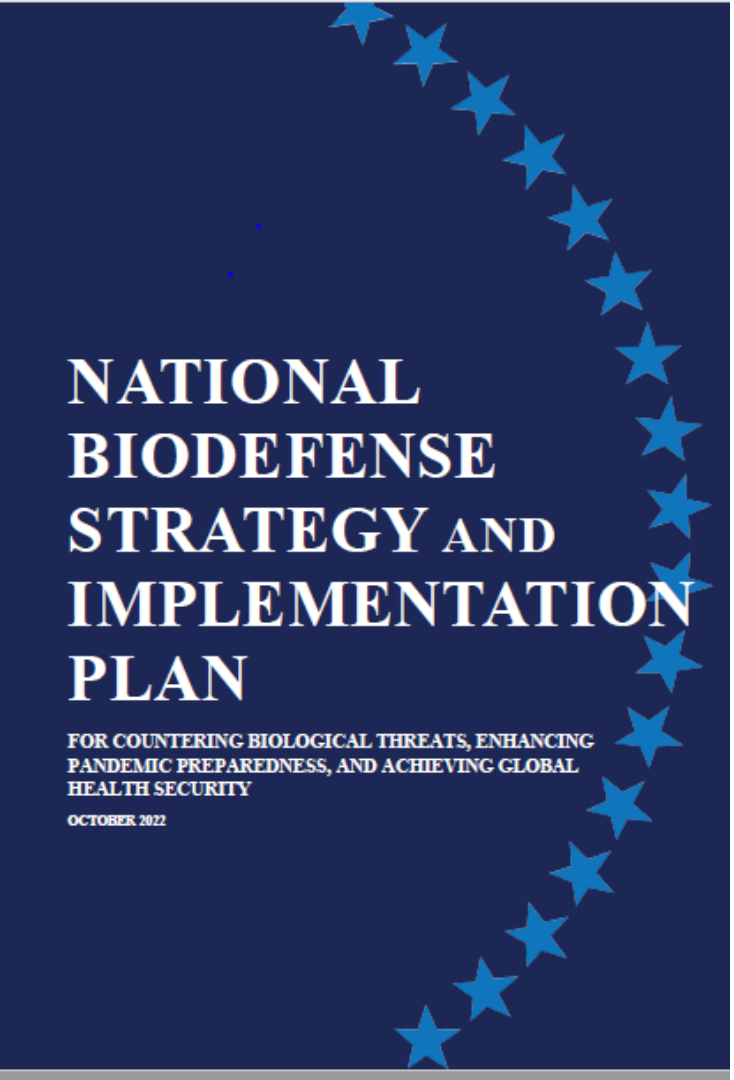
- Components for QbD Adoption
- Setting Expectations
- Team Recognition & Ownership of the Process
- QbD Principles Document
- Measurement for Individual Study Teams
- Perspectives for QbD Discussions & Potential Champions
- QbD Workshop Tools

CTTI's QbD Recommendations are foundational to all tools.

FDA Guidance Documents



- Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (final)- March 2020/ August 2021
- Multiple Endpoints in Clinical Trials (final) - October 2022
- Ethical Considerations for Clinical Investigations of Medical Products Involving Children (draft) - September 2022
- Design and conduct of externally controlled trials (draft) - January 2023



U.S. Biodefense Strategy

- Plan called for USG to maintain and build upon the domestic clinical trials infrastructure, *inclusive of international sites as appropriate*, to ensure readiness.
- Goal: administering candidate countermeasures to participants within 14 days of the identification of a viable countermeasure.
- The **White House Office of Science and Technology Policy** (OSTP) in partnership with the **National Security Council** is leading on this effort, with **HHS** support.

notice of filing a request with the Postal Regulatory Commission to add a domestic shipping services contract to the list of Negotiated Service Agreements in the Mail Classification Schedule's Competitive Products List.

DATES: *Date of required notice:* October 26, 2022.

FOR FURTHER INFORMATION CONTACT: Sean Robinson, 202–268–8405.

SUPPLEMENTARY INFORMATION: The United States Postal Service® hereby gives notice that, pursuant to 39 U.S.C. 3642 and 3632(b)(3), on October 20, 2022, it filed with the Postal Regulatory Commission a *USPS Request to Add Priority Mail Express, Priority Mail, First-Class Package Service, and Parcel Select Service Contract 72 to Competitive Product List.* Documents are available at *www.prc.gov*, Docket Nos. MC2023–23, CP2023–22.

Sarah Sullivan,

Attorney, Ethics & Legal Compliance.

[FR Doc. 2022-23318 Filed 10–25–22; 8:45 am]

BILLING CODE 7710–12–P

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

AGENCY: Office of Science and Technology Policy (OSTP).

ACTION: Notice of Request for Information (RFI) on clinical research infrastructure and emergency clinical trials.

SUMMARY: In accordance with the 2022 National Biodefense Strategy for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security (National Biodefense Strategy) and the American Pandemic Preparedness Plan (APP), the White House Office of Science and Technology Policy (OSTP), in partnership with the National Security Council (NSC), is leading efforts to ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies. Efforts in this area could include the establishment of a U.S.-level governance structure and outreach to a research into underserved communities, and increase diversity among both trial participants and clinical trial investigators. Building U.S. capacity to carry out emergency clinical trials will enlarge and strengthen the U.S. clinical trials infrastructure overall.

DATES: Interested persons and organizations are invited to submit comments on or before 5 p.m. ET on December 27, 2022.

ADDRESSES: Interested individuals and organizations should submit comments electronically to *emergencyclinicaltrials@ostp.eop.gov* and include "Emergency Clinical Trials RFI" in the subject line of the email. Due to time constraints, mailed paper submissions will not be accepted, and electronic submissions received after the deadline cannot be ensured to be incorporated or taken into consideration.

Instructions

Response to this RFI is voluntary. Each responding entity (individual or organization) is requested to submit only one response. Please feel free to respond to one or as many prompts as you choose.

Please be concise with your submissions, which must not exceed 8 pages in 12-point or larger font, with a page number on each page. Responses should include the name of the person(s) or organization(s) filing the comment.

OSTP invites input from all stakeholders, including members of the public, representing all backgrounds and perspectives. In particular, OSTP is interested in input from research institutions, clinical trialists, health care providers interested in clinical research, contract research organizations (CROs) and other clinical trial service providers, pharmaceutical and biotechnology companies, and community health care organizations. *Please indicate which of these stakeholder types, or what other description, best fits you as a respondent.* If a comment is submitted on behalf of an organization, the individual respondent's role in the organization may also be provided on a voluntary basis.

Comments containing references, studies, research, and other empirical data that are not widely published

response to this RFI may be posted on OSTP's website or otherwise released publicly.

In accordance with FAR 15.202(3), responses to this notice are not offers and cannot be accepted by the Federal Government to form a binding contract. Additionally, those submitting responses are solely responsible for all expenses associated with response preparation.

FOR FURTHER INFORMATION CONTACT: For additional information, please direct questions to Grail Sipes at 202–456–4444 or *emergencyclinicaltrials@ostp.eop.gov*.

SUPPLEMENTARY INFORMATION:

Background: Currently, the U.S. clinical trials infrastructure is not well prepared to carry out coordinated, large-scale clinical research in the event of an outbreak of infectious disease or other public health emergency. As was seen in the initial stages of the COVID–19 outbreak, different institutions and networks tend to implement their own research protocols and capture and store their own data. The lack of a coordinated approach to clinical trials research in emergency settings has slowed the development of actionable information, which has in turn delayed the availability of vaccines, therapeutics, and diagnostics; and may also impede the tracking of the outbreaks themselves. Without some mechanism to coordinate and organize research on a larger scale in an emergency setting, researchers and decisionmakers are left with a series of relatively small, often inconclusive studies, and assembling data for larger-scale analysis is challenging. In addition, and very significantly, our current approach to clinical research in the emergency setting excludes many patients and health care providers in underserved areas, and has contributed to a lack of diversity among clinical trial participants and among the investigators who lead clinical trials.

The National Biodefense Strategy calls for the U.S. government to maintain and build upon the domestic clinical trials infrastructure, with the addition of international sites as appropriate, to ensure readiness to "expedite the evaluation of safe and effective vaccines, therapeutics, and diagnostics for all segments of the population during a nationally or

OSTP: RFI in late 2022

- Governance (including best practices for designing trials i.e., quality by design)
- Identifying/incentivizing institutional participants
- Building diversity/equity
- Developing master agreement
- Addresses international trials

Data capture to be subject of separate RFI

FDA

International Coordination and Capacity

- G7 Health Ministers “Therapeutics and Vaccines Clinical Trials Charter” – June 2021
- World Health Assembly resolution – May 2022
- Quad Leaders Summit “Commitment to Pandemic Preparedness” – May 2022

“Perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away.”

—Antione de Saint-Exupéry