2020 Spring Regulatory Update and Hot Topics in Clinical Research

COVID-19: The Virus, Preparedness in the time of Crisis, and Clinical Research

PANEL 3

2:15pm – 3:15pm

Accelerated Clinical Trials – Adapting to the Pace

CTSI Clinical and Translational Science Institute at Children's National

A PARTNERSHIP WITH THE GEORGE WASHINGTON UNIVERSITY

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GHUCCTS

Georgetown-Howard Universities
Center for Clinical and Translational Science

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

Research During Covid-19: Accelerated Timelines and Regulatory Flexibility

Deb Paxton, MS, CIP
Director
Office of Human Research
The George Washington University

Challenges of Research During Covid-19

Acceleration towards a solution

Unique research opportunities

Maintenance of ongoing research

Reconfiguring risk vs. benefit

Acceleration Towards a Solution

- Research vs. Treatment
  - Expanded use options
  - Data considerations
- Prioritization
  - At the individual, departmental, organizational, and national levels
- Incrementation
  - Smaller = more flexible and more easily approved

Unique research opportunities

Demonstrating benefit

Prioritization

- People before the research
- Safety before the research

Parsimony

- Targeted research questions
- Intentional data collection
- Recognition of limited resources

Maintenance of Ongoing Research

Changing research procedures to keep participants and research personnel safe

Pivoting to accommodate restrictions

- Modifying research questions
- Communicating with sponsors

Changes considered under new risk/benefits in light of the crisis

Reconfiguring Risk vs. Benefit

New risks to participants

New risks to research personnel

Revised expected benefits - revisions to procedures or research questions may affect expected benefits from the research

Working with regulators

Federal agencies – flexibilities in requirements and official guidance

- Example: expanded use of convalescent plasma

Working with the IRB and IBC

- Prepared committees
- Guidance on options and timelines

Specificity of information and questions

School of Medicine & Health Sciences

THE GEORGE WASHINGTON UNIVERSITY

"DSMB in Real Time" during COVID-19 Pandemic & Response

David Diemert, MD

Professor, Depts of Medicine & MITM

Co-Chair, GW IRB

21 April 2020

smhs.gwu.edu

SMC/DSMB/DMC Roles

1. Periodically review and evaluate accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy

2. Make recommendations to Sponsor/Investigators about trial continuation, modification, or termination

DSMB/DMC Issues in COVID-19 Pandemic

- DSMB operations: for ongoing studies, can current board continue to support trial needs?
  - Member availability (other roles/responsibilities)
  - Teleconferencing capacity
    - Connectivity issues
  - Physical locations/time zones of members
  - Can routine or *ad hoc* meetings be convened and without delay?

- If not, new board/members?

DSMB/DMC Issues in COVID-19 Pandemic

- Sponsors/Investigators must assess if it is feasible to continue a trial in view of COVID-19 public health measures implemented to control the pandemic.

- Involvement of a study's DSMB, can provide support for these assessments:
  - A primary DSMB responsibility is assuring the trial participant safety
  - Board assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider

DSMB/DMC Issues in COVID-19 Pandemic

Factors for DMSB to consider re-study continuation:

- Do limitations imposed by COVID-19 on protocol implementation pose **new safety risks** to trial participants
  - Can these risks be mitigated by amending study processes and/or procedures?
- Are clinical investigator/sub-investigators available to provide trial oversight, and properly assess and manage safety issues?
- Are there sufficient trained clinical trial personnel given the evolving COVID-19 situation and its impact on staff availability?
- Is there adequate equipment/materials (e.g., PPE) for clinical trial personnel?

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

DSMB/DMC Issues in COVID-19 Pandemic

Factors for DMSB to consider re-study continuation:

- Will individual sites remain open for required in-person assessments or can investigator provide required in-person assessments at an acceptable alternate location(s)?
  - OR, can protocol-specified in-person assessments instead be conducted virtually?
- Availability of clinical trial supplies and continued operations of vendors, especially related to supply of IP and/or supplies essential to maintaining appropriate safety/efficacy monitoring or other key trial procedures.
  - Product stability (shelf life) if treatment schedule is revised
  - Can clinical site properly store the product for the needed duration?
- Continued availability and support for IT systems needed to support the trial (e.g., EDC).
  - Are contingency plans adequate for anticipated disruptions?
  - Can other plans be instituted to minimize potential disruptions?

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Accelerated Clinical Trials: Adapting to the Pace

Research Quality

Shaunagh Browning
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Director, Office of Research
Quality Assurance

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Subject Safety

Data Quality

Key Reasons for Poor Quality

- Inadequate staff training on GCPs and the protocol, mostly due to sudden increase or decrease in resources
- Poor (or lack of) management supervision or quality control of task completion during the study
- Lack of protocol clarity leading to poor understanding of what is required
- Lack of quality control over collection and recording of study data

(Bartekian, 2019)
https://www.socra.org/blog/quality-by-design-for-clinical-trials/

Quality Management Plan

- A Quality Management system includes defined quality requirements comprised of:
  - Site procedures
  - Forms and templates
  - Quality control (QC)
  - Quality assurance (QA)
  - Corrective and preventative action (CAPA) processes
  - Continuous quality improvement activities that support process standardization, data accuracy, completeness and data integrity

https://www.niaid.nih.gov/sites/default/files/qmppolicy_0.pdf

Quality by Design (QbD)

- Quality risk management approach
- Quality is built-in
- Focus on key risk indicator (KRI) data
  - event rates, number of protocol violations, query rate, percent of patients with dose reductions
- Assessment is ongoing part of trial design: recruitment to results
- Corrective actions are made early

(Landray et al., 2012)

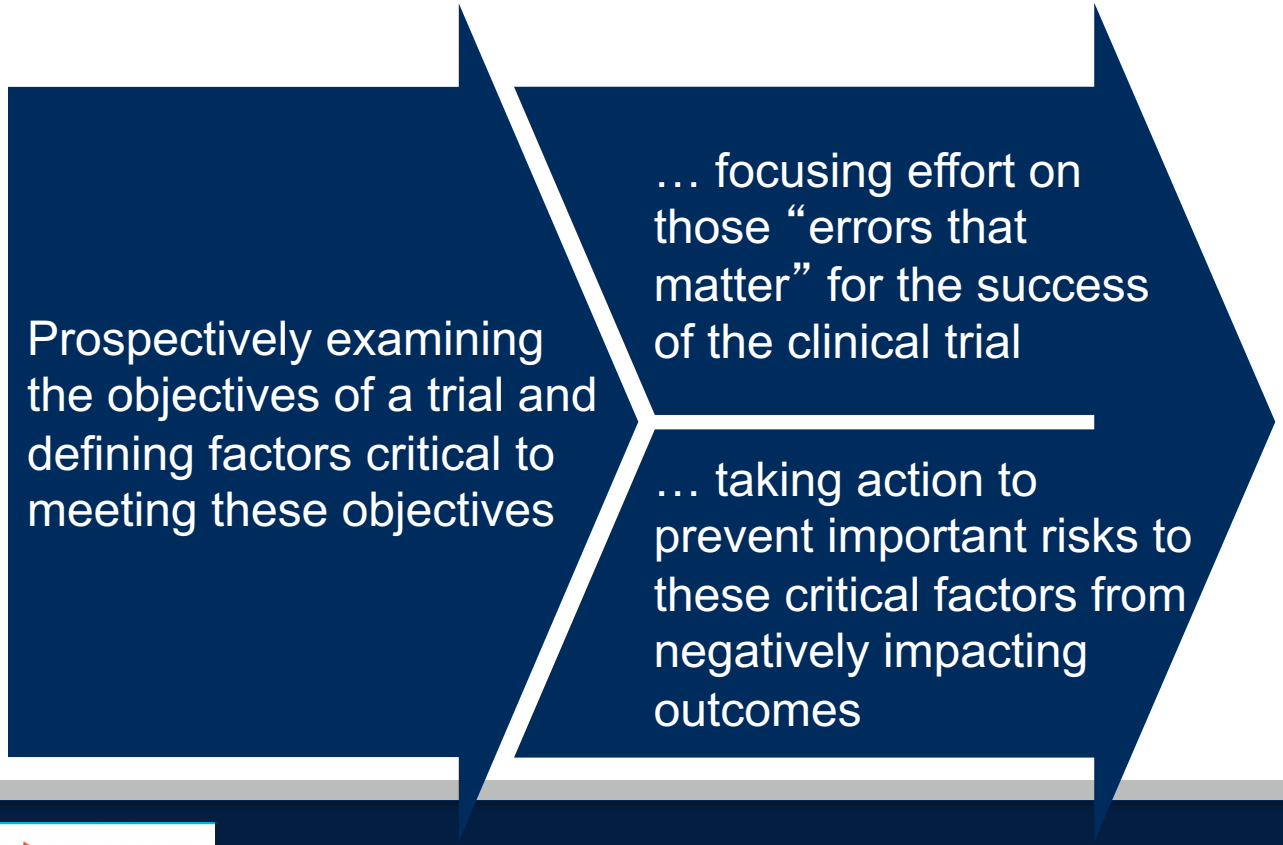
https://www.ctti-clinicaltrials.org/files/drug_information_journal-2012-landray-657-60.pdf

Quality by Design

"…trial quality is defined as the avoidance of errors that matter to decision making, and monitoring is repositioned as a tool for evaluation and improvement."
(Landray et al., 2012)

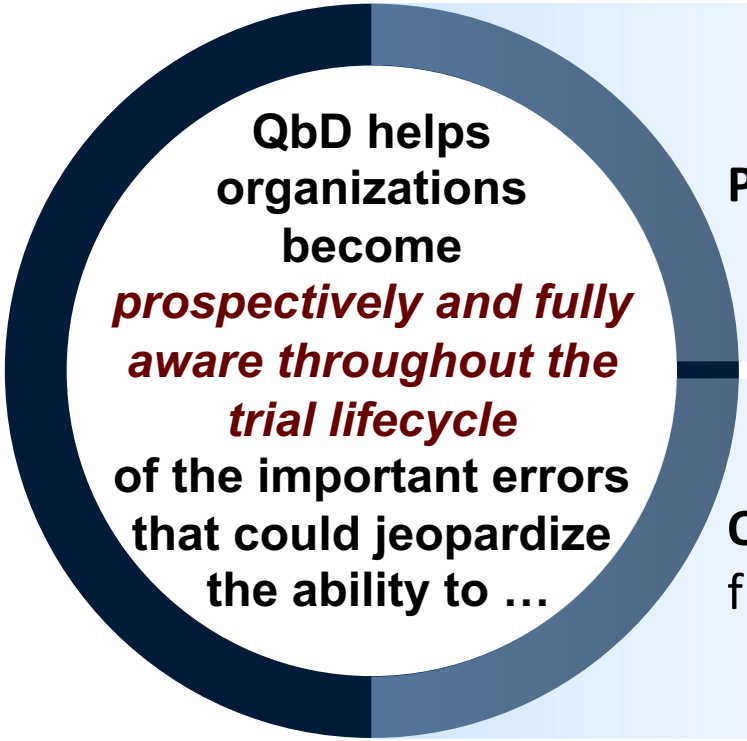
Quality by Design: QbD Defined

"Quality" in clinical trials is defined as the absence of errors that matter



Understanding what data and processes underpin a successful trial is essential to subsequently identifying and managing important and likely risks to **improve quality and outcomes for clinical trials**

How QbD Improves Clinical Trials



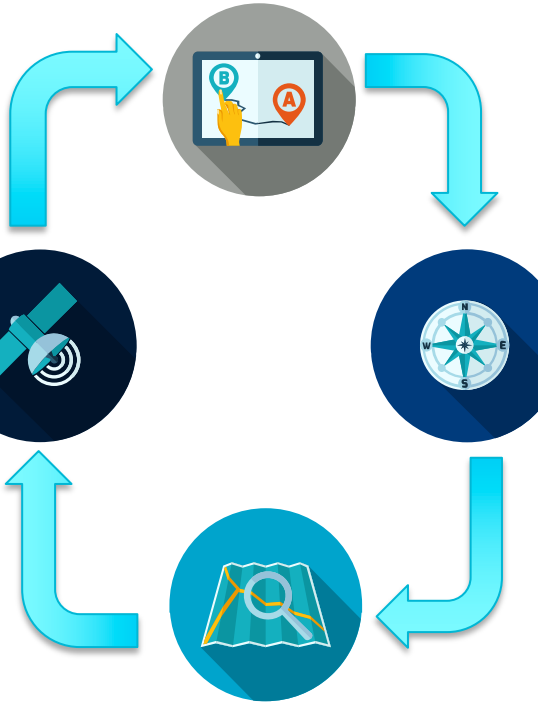
Protect patients during the trial

Obtain reliable results and meaningful information from the trial

QbD Implementation: Plan, Do, Check, Act

Build/plan quality into clinical trials from the beginning, focusing on what matters most

PLAN



DO

Implement study risk management strategies

CHECK

Monitor leading indicators of quality in the study

ACT

Systematically drive remediation and learning

Mitigate those risks that will likely lead to errors that matter and determine how to rapidly identify and react when there is an issue

Rory Collins, MBBS, MSc,
University of Oxford

"Undue emphasis has been placed on data accuracy when, in fact, reliable results can be obtained even from imperfect data."


Jamaica
2163
NETHERLANDS ANTILLES
1003
3317
USA
3152
Subject Safety
RECORD FINISH
Data Integrity

References

- Bartekian, V. (2019) Quality by Design for Clinical Trials. SOCRA Blog Retrieved from https://www.socra.org/blog/quality-by-design-for-clinical-trials/
- Landray, M., Grandinetti, C., Kramer, J., Morrison, B., Ball, L., & Sherman, R. (2012). Clinical trials: Rethinking how we ensure quality. *Drug Information Journal,*46 (6), 657-660. DOI: 10.1177/0092861512464372
- NIAID (n.d.) Requirements for Clinical Quality Management Plans (CQMP) Policy. Retrieved from https://www.niaid.nih.gov/sites/default/files/qmppolicy_0.pdf

Ethical Considerations in Accelerated Clinical Trials

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Pellegrino Center for Clinical Bioethics

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Overview

Research Ethics

Ethics in Public Health Crisis

Exceptional Circumstances

Uncertainty

Acceleration impact

Unproven Interventions

Research Ethics

Fundamental Premise

Ethics

- guides decisions and actions
- required more (not less) in dire circumstances
- a necessary framework in novel circumstances

Ethics in Public Health Crisis

A Matrix for Ethical Decision Making in a Pandemic Tuoey 2007

Ethics in Emergency Research

- scientifically valid and add social value
- risks are reasonable in relation to anticipated
- participants are selected fairly and participate voluntarily (informed consent)
- participants' rights and well-being protected
- studies undergo independent review

Did we learn from SARS/MERS/Ebola?

unanswered ethical questions:

- exceptional circumstances,
- unproven interventions,
- the goals of interventional research in terms of individual versus collective interests,
- the place of adaptive trial designs and
- the exact meaning of compassionate use with unapproved interventions.

The Brooklyn Hospital Center is on the front lines of the coronavirus pandemic.
Victor J. Blue for The New York Times

Do Exceptional Circumstances change the Paradigm ?

Randomized Control Trial or Compassionate Use

When Mortality is increasing…. why or why not Try?

Dealing with Uncertainty

Areas of Clinical Trials affected by Acceleration

- Accelerated Pace itself
- Adapted Design
- Independent Review
- Consent/ Therapeutic Misconceptions
- Information/Data Sharing

Additional Justice

- Recruitment/Compensation
  - Participants and selection- require equal value and respect
  - Health as an essential value

- Access-Ensure equitable access to resulting treatment
- Communicating results

Ethical use of Unproven interventions

1) no proven effective treatment exists;

2) not possible to initiate clinical studies immediately;

3) data providing preliminary support of the intervention's efficacy and safety are available;

4) ethics committee approval;

5) risks can be minimized;

6) informed consent and

7) the emergency use of the intervention is **monitored** and the results are **documented** and **shared**

ie. "monitored emergency use of unregistered and experimental interventions" (MEURI).

WHO 2016 Ethics in Infectious Disease Outbreak

“maximize the contribution that scientifically robust, ethical research can make to improving the health of people affected by emergencies. “

Nuffield Council on Bioethics

References

- Calain (2018) The Ebola clinical trials: a precedent for research ethics in disasters. J Med Ethics 2018;44:3–8. doi:10.1136/medethics-2016-103474

- Nuffield Council on Bioethics (2020) Research in Global Health Emergencies.

- Tuohey (2007) A Matrix for Ethical Decision Making in a Pandemic. Health Progress. A Matrix for Ethical Decision Making in a Pandemic (/docs/default-source/health-progress/a-matrix-for-ethical-decision-making-in-a-pandemic-pdf.pdf?sfvrsn=2)

- World Health Organization (2016) Guidance for Managing Ethical Issues in Infectious Disease Outbreaks