Session 1: Sponsor Oversight in Clinical Trials

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
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Sponsor role and oversight responsibilities in global clinical trials, including those trials incorporating novel designs, operational approaches, and data sources (RWD/RWE)

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Overview

- Clinical trials Global status
- New trial designs
- Sponsor oversight
- Verification of compliance
- ICH Update

Sponsor Obligations

- Responsible for the overall conduct of the trial
- Can delegate tasks to third parties
- Can not delegate responsibilities
- Responsible for compliance with applicable regulations

Global status of Clinical Trials

Clinical Trials are becoming more complex:

- Novel design trials (e.g. adaptive trial design)
- More trials utilizing Real World Data (RWD) and Real World Evidence (RWE)
- More trials adopting Artificial Intelligence (AI) and Machine Learning (ML)

What is new in ICH E6 (R3) for trials design

- Type and design of the trial

  Adaptive design, platform/umbrella/basket, decentralized trials (to be added)

- Criteria for Discontinuation of the trial

  dose adjustment and dose interruption (to be added)

- Identification of data entered in Case Report Forms (to be removed)

Novel trials: Adaptive design trials

- Is a design that allows for planned modifications

- Is a seamless design that allows for planned changes

- Modifications can not take place at any given time

- Modifications and adaptations have to be pre-planned

Types of Adaptive design trials

- Adaptive randomization design
- Group sequential design
- Adaptive dose finding design
- Adaptive treatment-switching design

Advantages of Adaptive design trials

- Flexibility
- Efficiency
- Ability to stop the study earlier if proved to be non-effective
- Better understanding of drug effects
- More acceptable to stakeholders

Comparing Conventional versus Adaptive study design

- Conventional study has rigid yet simple study design
- Adaptive design has a flexible yet complicated design
- For conventional study Phases I–II are well defined while for adaptive can be seamless phase 2/3 design
- For conventional study, regulatory view is well endorsed while for adaptive designs, is still speculative

Limitations of Adaptive design trials

They may require specific analytical methods that may not be readily available

Some efficiency in some aspects of the design but losses in another aspects

Introduction of logistical challenges

Challenges in interpretability of results

Sponsor Oversight

Adaptive Design Trials

- Quality of the design of the clinical trial
- Ensure trial processes compliant with the protocol
- Determine criteria for protocol deviations
- Decisions impacting subjects' safety and data integrity

Sponsor Oversight (cont'd)

Adaptive Design Trials

- Selection of qualified individuals
- Prompt in implementing Corrective and Preventative Actions (CAPA)
- Establish Independent Data Monitoring Committee (IDMC) to assess safety data
- Establish endpoints
- Committees recruited should have SOPs

Verification of Compliance

Adaptive Design Trials

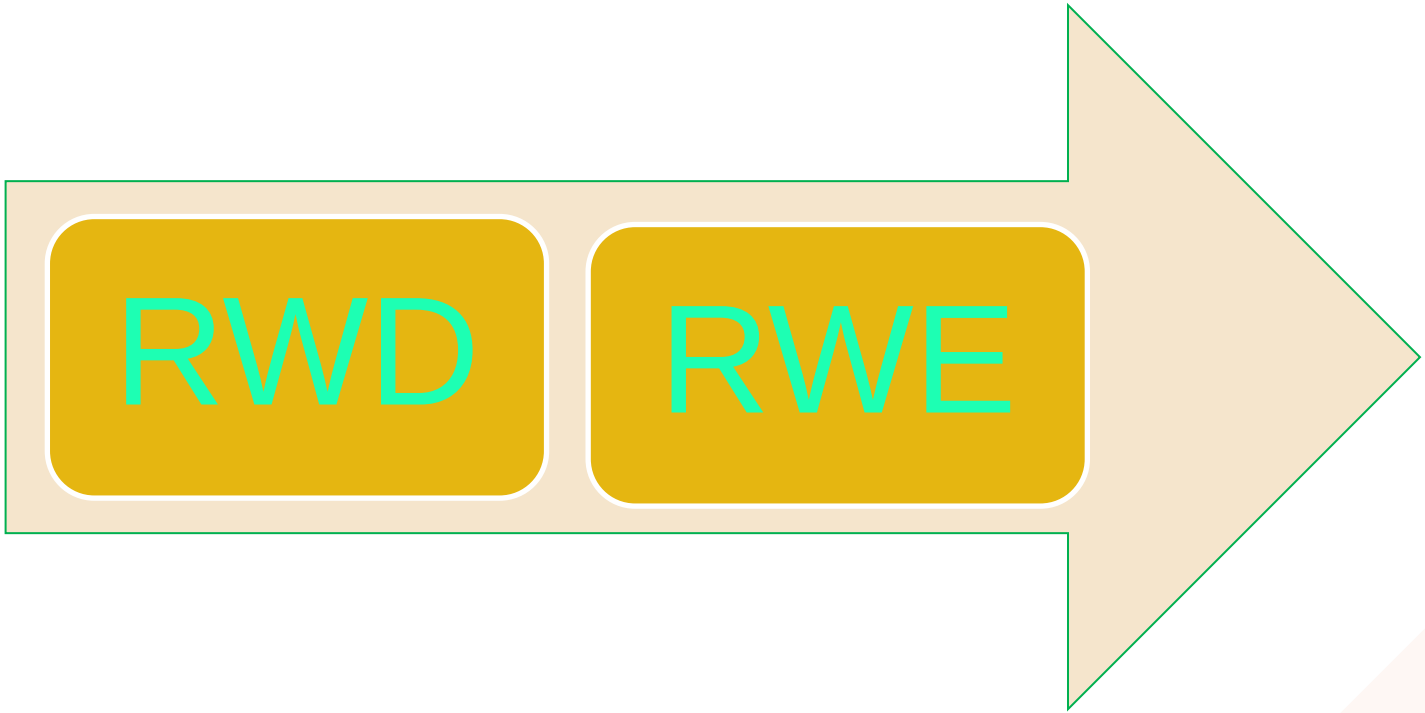
- Verify the design is approved by the regulator
- Verify the approved design is followed by the site
- Verify the design is applied to all sites
- Verify the REB was informed and/or approved the design
- Verify monitoring of the design is applied to all sites

RWE and RWD

- Real World Evidence (RWE) is evidence about the use and potential benefits or risks of a medical product

- This evidence comes from analysis of Real World Data (RWD) which is data relating to patient status and/or the delivery of health care routinely collected from a variety of sources

Real World Data/Real World Evidence



Benefits of RWD in clinical trials

- Gain insight into public health, advance health care
- Increase drug access for specific patient populations
- Increase trials feasibility. Data collected from clinical trials has limitations

Sponsor Oversight

RWE/RWD

- Identify it in their cover letter
- Explain why RWE/RWD is being used
- Explain how RWE/RWD was gathered
- Demonstrate how potential biases were mitigated

Verification of Compliance

RWE/RWD

ICH Update – adaptive clinical trials

- Currently new topic
- No full harmonisation between some regulators
- Working on developing a new ICH guideline
- Anticipated completion date is January 2025

Questions?

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Expanded use of Contractors and Service Providers in Clinical Trials

- *Oversight Obligations*
- *Written Agreements*
- *Case Studies*

Contract Services in Global Clinical Trials

Traditional

- Site Selection & Monitoring
- Central Laboratory Testing
- Test Article Management and Distribution
- Data Management
- Statistics & Medical Writing

Growth Areas

- Site Management Organizations
- Remote Data Acquisition through Digital Health Technologies and cellular communications (e.g., eDiaries, tablets, phone apps)

ICH E6(R2) – Section 5.2 Contract Research Organization (CRO)

- Sponsor may transfer but retains ultimate responsibility
- Transfers should be in writing
- Sponsors should ensure oversight
- Duties and functions not specifically transferred to *and* assumed by a CRO are retained by the Sponsor

Considerations for Contracted Services in Global Clinical Trials

- Well-written Contracts and Study Plans
- Training, Communication and Oversight
- Study Data must be Organized, Accessible for Regulatory Review, and meet ALCOA Standards

Contractor Agreements in Global Clinical Trials

- Are all critical roles and responsibilities defined and assigned in contracts, agreements or plans?
- Has the Sponsor assured adequate control?
  - Are training plans and key documents reviewed by the sponsor?
  - Does the vendor have authority to sub-contract tasks or make changes to the study plan?
- Does the Sponsor retain access to all source data or are there limits to oversight activities?

Vendor Oversight

- Have all hazards to subjects and data been identified and controlled in the plan for services?
- Are site selection visits or vendor audits prior to signing the contract and a data audit at the end of study alone adequate? Does it depend on the tasks delegated?

Example: Digital Health Technologies

- Define source data and assure access for sponsor and regulatory oversight (including all metadata)
- Assure all clinical and privacy risks addressed (Risk Management and Safety Monitoring Plans, Vendor and Site Training Plans, protocol and/or contract)
- Assure adequate Verification, Validation and Usability Evaluations of devices (intended use, patient population, accuracy & precision, accessibility)

Record Retention and Availability

- Investigator records
  - All Subject-Level Data – observations, tests, assessments, treatments, etc.
  - Blinded Vendor Data and eCRFs should be provided by close of the trial
- Sponsor records
  - Investigational Plans, Policies & Procedures, Training & Qualifications, Regulatory Correspondence, Contracts, Monitoring and Safety, etc.

Case Studies

Contract Monitor

- Vendor failed to meet schedule of visits and scope of coverage was limited
- Site non-compliance was not identified in time to secure effective corrective actions or to terminate non-compliant sites.
- Ineligible subjects were enrolled and treated at multiple sites
- Over- and Under-dosing errors occurred at multiple sites
- Training provided to sites by the contractor was inadequate
- Final data set included ineligible and improperly dosed subjects' data.

Site Selection & Data Management

- Sponsor retained responsibility for monitoring
- Clinical Investigator refused access to source data under regional privacy legislation – no source data monitoring or inspection was permitted.
- Study Data were not provided by investigators in a format compliant with regulatory standards for electronic records.

PRO Vendor - eDiaries

- Patient Reported Outcomes – symptom diaries were maintained electronically through a vendor
- CI could see sequential eDiary entries live and identify missed reports from subjects & alert emails were autogenerated
- Retrospective entries were via paper submissions, transcribed to the dataset

PRO Vendor – eDiaries (cont.)

- CI failed to retain missed entry notification emails and failed to solicit and/or reconcile retrospective entries
- Retroactive reports were incomplete and no attempts to resolve were documented
- Was the plan for use of eDiaries complete and adequate to assure data integrity?

Summary

- Sponsors often must rely on multiple contractors to conduct a global clinical trial
- Detailed, well-designed contracts and study plans are essential
- Sponsors remain ultimately responsible
- Training and Vendor Oversight are key

Resources

- Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- Guidance for Industry: Electronic Source Data in Clinical Investigations

Questions?

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Risk-proportionate Sponsor oversight in an evolving clinical trial environment

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Overview

- Regulator vs Sponsor adoption of risk adaptation
- Evolution of sponsor oversight
- Discussion of risk proportionate sponsor oversight measures

Regulatory expectations

- Sponsor is responsible for the trial and therefore how it is conducted
- Long standing regulatory acceptance of risk-adaptation
- Risk averse sponsors?
- Change in regulatory expectation from risk-adaptation optional → requirement

Continuing evolution

- ICH E6 R3 & UK Clinical Trial Regulation consultation
  - Expect risk identification by the sponsor
  - Expect proportionate and risk appropriate approaches
  - Implementation of quality by design
  - Reduce unnecessary burden
  - Support flexibility

ICH E6 R3 – Principle 7

"Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected.

7.1 Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results."

ICH E6 R3 – Principle 7 (2)

- *“7.2 The focus should be on the risks to participants beyond those associated with standard medical care. The risks relating to investigational products that have a marketing authorisation when used in the clinical trial context may differ from the routine care of patients and should be taken into consideration.*
- *7.3 Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun.”*

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

Proportionate approach to oversight

- Not all trials are the same!
- Shift in focus onto the reliability of results rather than data perfection
- Risk-based quality management at both trial and organisational level

Importance of risk assessment

- Identification of key factors (activities/data) that impact:
  - participant safety
  - trial results
  - data integrity

- Proposal of appropriate and adaptive mitigations to protect the identified factors

Ongoing risk management

- Not a ‘point in time’
- Need to:
  - actively manage identified risks
  - assess continued suitability of mitigations
  - assess effectiveness of risk control strategies
  - suitably documented

Risk based oversight considerations

- Nature of the trial – pivotal / supportive
- Trial design and complexity
- IMP being used
- Trial endpoints
- Interventions
- Participant population
- Sponsor / service provider / investigator experience

Complexity

- Vendors
- Technology
- Assessments
- IMP
- Interactions
- Sequencing
- Location

Sponsor expectations – systems

- Management support for risk proportionate approaches
- Quality system enshrines risk proportionate approaches
  - SOPs
  - Audits
  - Training

Sponsor expectations – trial specific

Oversight strategy

- Protocol (e.g. critical to quality factors, science, recruitment etc)
- Vendor management
- Plans (communication, monitoring, data, safety etc)
- Charters
- Monitoring approaches
- Audit strategies

Ongoing risk review

- Common to see initial risk assessment
- Lack of ongoing risk review
  - Protocol amendments
  - Changes to the trial
  - Changes to supporting processes
  - Changes to vendors or systems

What does effective risk proportionate sponsor oversight look like?

- Clear understanding and knowledge of:
  - the key factors
  - the mitigations
  - how the trial fits together
  - the ‘moving parts’ and interactions
  - potential impacts on participant safety and data reliability

What does effective risk proportionate sponsor oversight look like? (2)

- Ongoing documented risk review
- Ongoing documented oversight and decision making
- Staff/organisational knowledge
- Empowered to adopt risk proportionality
- Empowered to act

Summary

- Understanding of the trial purpose, intended conduct and outcomes is essential
- Promote flexibility based on the individual trial
- Wide ranging risk assessment – get into the detail!
- Ongoing risk assessment

Closing thought

It is time for sponsors to adopt risk proportionality knowing that there is support from the Regulators for its use.

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