ICH E6: Good Clinical Practice
- stick to the principles -

Martin Landray

Nuffield Department of Population Health, University of Oxford

European Society of Cardiology Regulatory Affairs Committee

Lead, Joint Initiative for Good Practice in Clinical Research

(supported by Wellcome Trust, Bill & Melinda Gates Foundation, African Academy of Science)

Need for reliable evidence from clinical trials

- Essential for making appropriate decisions concerning the benefits and harms associated with clinical interventions.
- Decisions made in the absence of reliable evidence
  (either because relevant trials have never been performed or because those that have been performed were inadequately designed, conducted, analyzed, or reported)
  may harm individual patients and public health.

Good Clinical Practice for Clinical Trials

Focus on the “Why”- not who, what, where , or how

- **Guiding Principles** (the constant reference point)
  - Protect the well-being of study participants
  - Ensure the reliability of the results (for benefit of future patients)
- **Approach to Quality**
  - Quality by Design (focussed on protocol)
  - Proportionate (by comparison with usual clinical care)
- **Operational Considerations**
  - Based on current E6 Principles and CTTI QbD Principles Document

Guiding Principles

- **Protect the rights, safety & wellbeing of study participants**
  - appropriate ethics approval
  - safe administration & monitoring of investigational products
  - safe study procedures & investigations
- **Ensure reliability of the results (for the benefit of patients)**
  - detect and quantify the efficacy and safety of treatment

Approach to Quality

- “Clinical trials should incorporate quality in their scientific and operational design, conduct and analysis.”

  www.ctti-clinicaltrials.org/files/Monitoring/Monitoring-Recommendations.pdf

- **Protocol:**
  - Quality starts with a well-articulated protocol
  - Quality Management should focus on delivering the protocol (with monitoring highlighting issues and enabling improvement)

CTTI

CTTI Quality-by-Design Project 2011-2015

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

i.e. errors which have a *meaningful impact* on the safety of trial participants or the credibility of the results (and thereby the care of future patients)

CTTI Quality by Design Recommendations 2015
www.ctti-clinicaltrials.org/qbd

CTTI

Quality Management

"The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials"

"The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected."

ICH E6 (R2) 2016

Examples that promote a proportionate approach to trial quality

- Clinical trials should be scientifically sound, and described in a clear, detailed protocol (E6 2.5)
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) (E6 2.8)

Examples that create confusion & caution

Serious Adverse Event:

"Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization…"

***ISSUE*:** "serious" ≠ "severe"

Adverse Drug Reaction:

"… a causal relationship between a medicinal product and an adverse event is at least a reasonable probability, i.e., the relationship cannot be ruled out."

***ISSUE*:** "is at least a reasonable probability" ≠ "cannot be ruled out"

Improving GCP guidelines to deliver reliable results

- Reliable answers do not require “perfect” data (if such a thing exists)
- Highlight key issues that influence results:
  - allocation concealment & randomisation
  - adherence to follow-up / “withdrawal”
  - ascertainment of outcomes
  - inappropriate unblinding of results
- Rational approach to safety monitoring (with emphasis on randomised comparisons rather than crude “relatedness” assessments)
- Ensure definitions are clear and consistent

Improving GCP guidelines to ensure participant well-being

- Recognise that many trials pose only a minimal additional risk to participant safety compared to normal clinical practice (tailor consent, data collection, and clinical monitoring accordingly)
- Proportionate consent processes that *inform participants* (rather than collecting paper or protecting the institution)
- Consider major safety issues (from drug or investigations), and appropriate ways to avoid, mitigate, or monitor (consider what is different from routine care)

Improving GCP guidelines to foster innovation

- Emphasise the principles & considerations
- Allow trialists to determine efficient & effective solutions
- Discourage excessive, defensive practice (e.g. oversight)
- Essential Documents are not always essential or documents

EU Clinical Trials Regulation (536/2014)

There is much to like:

- Accommodates "low-intervention clinical trial" and risk-proportionate processes (including data collection, monitoring, AE reporting, trial master file)
- Deals appropriately with consent in different circumstances (e.g. incapacity, minors, pregnancy, emergencies)
- Emphasises need for suitable facilities and appropriately trained staff
- Acknowledges and accommodates co-sponsorship (provided well documented)
- Acknowledges that principal investigators are responsible for ensuring compliance of a clinical trial at their site but may assign tasks among members of the team

GCP Guidelines:
Careful drafting and thoughtful application are essential

- It is fully recognised that many historical complaints about GCP are as much caused by excessive, unthinking application or over-interpretation as by poor drafting of the guidelines themselves
- It is thus critical that the drafting of guidelines includes the full range of stakeholders who will be involved in their subsequent use

The Future for Good Clinical Trials Guidelines

- *Aim:* Rational & proportionate GCP guidelines which enable timely, affordable & high quality assessment of the benefits & harms of health interventions
- Based on key scientific & ethical principles
  - focused on issues that materially influence the well-being of trial participants & reliability of the results
- Clear, concise, consistent & proportionate
  - recognise the risks associated with usual clinical practice & lack of reliable evidence on treatment effects
- Co-developed through an *Open Regulatory Science* approach
  - involving regulators, funders, commercial & academic trialists, clinicians, patients & public
- Forward looking: Foster innovation in health interventions & trial methods
  - e.g. take advantage of digital technology, data analytics & genomics
- Broadly applicable, widely adopted & durable
  - across disease areas, intervention types, development phases, trial designs, geographies & time

goodtrials@wellcome.ac.uk