Sensible Guidelines for randomised clinical trials

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on behalf of
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Background

- Increasing regulation and trial-related bureaucracy
- Clinical trials much more difficult and costly to conduct
- Important research being hindered

Sensible Guidelines for the Conduct of Clinical Trials

- Forum established by trialists at Oxford, Duke and McMaster Universities
- Aim to identify ways in which to remove unnecessary obstacles to clinical trials
- Involves academic groups, regulators, funders, pharmaceutical companies and patient representatives
- 3 international meetings: 2007, 2009, 2012

Trial regulatory environment: current problems

Trial aspect	Problem
Approval	Complex; costly; heterogeneous; time-consuming
ICH-GCP	Inflexible; frequently over-interpreted; undue emphasis on relatively unimportant aspects of trials (at expense of key aspects)
Monitoring	Undue focus on retrospective source data verification
Safety reporting	Undue focus on individual case reports
Cost	Trials are becoming prohibitively expensive
Consent	Over-complicated; difficult in emergency situations

Clinical trial approval

- The need to obtain approval from multiple bodies before starting clinical trials leads to substantial delays
- Even where centralised trial authorisation procedures have been adopted (e.g. in UK), significant hurdles remain
- Problems exacerbated when trials involve more than one country

ICH-GCP

- Intended to safeguard the safety and rights of participants in trials and to ensure the reliability of trial results
- Often over interpreted and implemented in ways that have become unnecessarily obstructive
- Not based on clear understanding of key principles that underlie trials which involve randomisation and control groups

Monitoring: need change in focus

- Typically undue emphasis on relatively unimportant aspects and source data verification
- Instead should focus on quality and aspects of trials most relevant to the rights and safety of patients and reliability of the study results e.g.
  - assessing the consent procedures
  - integrity of the randomisation process
  - completeness of follow-up
- Aim to detect important problems early in a trial rather than retrospectively

Safety reporting

- SUSAR reporting a regulatory requirement
- Events typically reported on a case-by-case basis
  - No meaningful denominator
  - Often only for participants in the active treatment group (no corresponding events for the control group)
- Can only reasonably be expected to detect large adverse effects on rare outcomes strongly associated with drug exposure (e.g. Stevens Johnson Syndrome, angioedema)
- More effective strategy for safety monitoring in trials = appropriate use of DMC

Is there any good news?!

Move to risk-based approach

- Use of risk-based approach endorsed by multiple parties:
  - FDA : Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring (August 2011)
  - MRC/DOH/MHRA joint project: Risk-Based Approaches to the Management of Clinical Trials of Investigational Medicinal Products (October 2011)
  - EMA: Reflection paper on risk based quality management in clinical trials (August 2011)

FDA: revised safety guidance

- FDA issued revised guidance and an amendment to its safety reporting requirements
- Aim to reduce current levels of uninformative over-reporting of serious adverse reactions
- Reporting need only be expedited if there is a reasonable probability (not just a possibility) that study drug caused the event
- Distinguishes between where it is appropriate to submit individual case reports (e.g. Stevens Johnson) and cases that should be aggregated and compared to a control group

Repeal of EU Clinical Trials Directive

- European Union 2001 Clinical Trial Directive : “EU-CTD”
- Intended to facilitate trials across Europe and better protect the public
- Widely recognised that has not met its goals
- July 2012: European Commission issued a proposal to replace the EU-CTD by a single Regulation that would be obligatory in all EU member states

EU proposed regulation
... some criticisms

- Directed more towards measures for expediting trial initiation rather than for facilitating overall trial conduct and oversight
- Still inappropriate emphasis on single case reporting for safety
- Rules for trial conduct and monitoring remain prescriptive and based on ICH-GCP

Proposed EU Regulation
… some key improvements

- Single portal for EU trial authorisations
- Measures to decrease indemnity costs
- More flexibility for consent in emergency situations
- More risk-based approach: less burdensome rules and shorter approval timelines for trials described as “low intervention”

Move to revise or replace ICH-GCP

- Sensible Guidelines May 2012 proposals:
  - Development of set of Q&As for appropriate interpretation of ICH GCP
  - Producing a revised version of ICH-GCP
  - Development of authoritative new “good clinical practice” guidelines

Summary

- Many problems remain
- However, meaningful progress being made
- Requires support from all of the relevant stakeholders, including academia, industry, regulators and patient representatives
- Need to keep up momentum for further change

Website

A series of papers published after the 2008 meeting about various aspects of running trials can be found at:

http://ctj.sagepub.com/content/5/1/38.citation)

Slides and audios from the 2012 meeting can be found at: http://www.cannectin.ca/default.cfm?id=136.