Sensible Guidelines for randomised clinical trials

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on behalf of
The Sensible Guidelines Group
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
# Trial regulatory environment: current problems

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