More Trials

to do more trials better
MoreTrials

A public campaign to make it much easier to do randomised trials in medicine

Created by trialists from Oxford with The James Lind Library, & Sense About Science

It started on 1st January, 2016
A paradox exists in medicine

Awareness of value of evidence from randomised trials

Ease of getting randomised trials done
This has only happened in the last 20 years, but only in medicine.

And in medicine 20 years ago we created: ICH-GCP.
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current Step 4 version
dated 10 June 1996

(including the Post Step 4 corrections)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.
ICH-GCP is NEITHER an international:

1. Ethical standard
2. Scientific Quality standard
We don’t need another ethical standard

We already have one!

The Declaration of Helsinki

Which is universally used and regularly reviewed and updated.
Why has ICH-GCP FAILED as a “scientific quality standard”
But, we have a TWINFOLD problem:
Problem #1

ICH-GCP
Problem #2

ICH itself
MoreTrials

To REPLACE ICH-Good Clinical Practice (ICH-GCP)

with a modern set of principles of how to do a randomised trial well

developed by everybody in the trial community
Progress in first year
Organisations (8) Supporting MoreTrials

http://moretrials.net/supporters/
More than 200 trialists from 28 countries

http://moretrials.net/supporters/
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Harmonised Guideline

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current Step 2 version
dated 11 June 2015

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the ICH regions (the European Union, Japan, the USA, Health Canada and Switzerland) for internal and external consultation, according to national or regional procedures.
Updated open Letter to EMA & ICH: From 5 research organisations and an international consortium of 119 health researchers in 22 countries

Signatories listed at end:

To: European Medicines Agency (EMA)
ich@ema.europa.eu
International Council on Harmonisation (ICH)
step2comments@ich.org

26th February, 2016

Co-ordinated response to the consultation by the International Council for Harmonisation (ICH) on its proposed E6 (R2) “Integrated Addendum” to the ICH E6 Guideline for “Good Clinical Practice”

The new EU Clinical Trial Regulation that was adopted in 2014 is intended to create a regulatory environment in Europe that promotes the conduct of clinical trials (which have declined in number following introduction of the 2001 EC Clinical Trial Directive) while ensuring appropriate protection for clinical trial participants. It refers to the ICH-GCP (International Council for Harmonisation Good Clinical Practice) guideline as a quality standard for clinical trials.

Along with many others, we have previously pointed out the serious problems with the ICH-GCP guideline. In particular, it places undue emphasis on less important aspects of clinical trials (e.g. source data verification) at the expense of those aspects of clinical trials (such as randomisation processes, follow-up completeness, risk-proportionate monitoring, and focused safety reporting) that have important implications not only for the safety of participants in clinical trials, but also for the reliability of the results of clinical trials and the consequent safety of future patients.

Moreover, a lack of flexibility in the ICH-GCP guideline and its interpretation (for example, a failure to recognise properly different levels of risk for participants in different types of trial) has resulted in clinical trial processes that are unnecessarily complex and expensive, as well as seriously hindering the adoption of innovative approaches to their conduct. As a result many clinical trials that should get done are not undertaken, and those that are started quite frequently fail to complete or provide reliable answers. Consequently, in our view, the current ICH-GCP guideline is not a suitable quality standard for the design, conduct, analysis or reporting of clinical trials.

Given these concerns, we welcomed the recent acknowledgement by ICH of the problems with its GCP guideline, and its decision to consult on proposals for change. However, for the reasons set out below, the changes proposed by ICH will do little to improve the regulatory environment for the conduct of clinical trials both in Europe and around the world.
Current challenges: Recent progress with regulations and their application

Researcher Perspective

Martin Landray
Professor of Medicine & Epidemiology
University of Oxford
martin.landray@ndph.ox.ac.uk
Problems still in ICH-GCP update: #1/4

The update to ICH-GCP still focuses on things that don’t matter (data checking/admin)
High quality DATA ≠ Reliable RESULT
Reliable RESULT ≠ High quality DATA
<table>
<thead>
<tr>
<th>Type of event</th>
<th>Simvastatin allocation (n=10269)</th>
<th>Placebo (n=10267)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simvastatin better</td>
<td>Placebo better</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>492 (4.8%)</td>
<td>743 (7.2%)</td>
<td>0.65 (0.58–0.73)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>547 (5.3%)</td>
<td>687 (6.7%)</td>
<td>0.79 (0.71–0.88)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>988 (9.6%)</td>
<td>1350 (13.1%)</td>
<td>0.72 (0.66–0.78)</td>
</tr>
<tr>
<td><strong>Strokes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>487 (4.7%)</td>
<td>621 (6.0%)</td>
<td>0.77 (0.69–0.87)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>82 (0.8%)</td>
<td>105 (1.0%)</td>
<td>0.78 (0.58–1.03)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>550 (5.4%)</td>
<td>700 (6.8%)</td>
<td>0.77 (0.69–0.87)</td>
</tr>
<tr>
<td><strong>Revascularisations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>487 (4.7%)</td>
<td>667 (6.5%)</td>
<td>0.72 (0.64–0.81)</td>
</tr>
<tr>
<td>Non-coronary</td>
<td>492 (4.8%)</td>
<td>559 (5.4%)</td>
<td>0.87 (0.77–0.98)</td>
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<tr>
<td>Any revascularisation</td>
<td>943 (9.2%)</td>
<td>1166 (11.4%)</td>
<td>0.79 (0.73–0.86)</td>
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<tr>
<td>ANY MAJOR VASCULAR EVENT</td>
<td>2187 (21.3%)</td>
<td>2765 (26.9%)</td>
<td>0.77 (0.72–0.81)</td>
</tr>
<tr>
<td>Type of event</td>
<td>Simvastatin allocation</td>
<td>Placebo allocation</td>
<td>Risk ratio &amp; 95% CI</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td></td>
<td>Simvastatin (n=10269)</td>
<td>Placebo (n=10267)</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>357 (3.5%)</td>
<td>574 (5.6%)</td>
<td>0.62 (0.54–0.70)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>587 (5.7%)</td>
<td>707 (6.9%)</td>
<td>0.82 (0.74–0.92)</td>
</tr>
<tr>
<td><strong>Any coronary event</strong></td>
<td>898 (8.7%)</td>
<td>1212 (11.8%)</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td><strong>Strokes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>366 (3.6%)</td>
<td>499 (4.9%)</td>
<td>0.72 (0.63–0.83)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>96 (0.9%)</td>
<td>119 (1.2%)</td>
<td>0.80 (0.61–1.05)</td>
</tr>
<tr>
<td><strong>Any stroke</strong></td>
<td>444 (4.3%)</td>
<td>585 (5.7%)</td>
<td>0.75 (0.66–0.85)</td>
</tr>
<tr>
<td><strong>Revascularisations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>513 (5.0%)</td>
<td>725 (7.1%)</td>
<td>0.70 (0.62–0.78)</td>
</tr>
<tr>
<td>Non-coronary</td>
<td>450 (4.4%)</td>
<td>532 (5.2%)</td>
<td>0.84 (0.74–0.95)</td>
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<tr>
<td><strong>Any revascularisation</strong></td>
<td>939 (9.1%)</td>
<td>1205 (11.7%)</td>
<td>0.76 (0.70–0.83)</td>
</tr>
<tr>
<td><strong>ANY MAJOR VASCULAR EVENT</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>0.76 (0.72–0.81)</td>
</tr>
</tbody>
</table>
Problems still in ICH-GCP update: #2/4

The update to ICH-GCP still focuses on things that don’t matter and STILL OMITS those few key principles that do matter.
Staff Training: It’s not painting-by-numbers

“ITT can’t be correct, or it would have been included in ICH-GCP”

“ITT and avoiding missing outcomes is not consistent with statements in ICH-GCP about patient withdrawal.”
Problems still in ICH-GCP update: #3/4

The update doesn’t fix the confusion in key definitions across different trial regulations.

(remember ICH has “harmonisation” in its name)
Definition of trial “Sponsor”

ICH GCP:
“An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.”

US 21 CFR 312.3:
“Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.”

EU Clinical Trials Regulation:
“Sponsor means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial.”
Problems still in ICH-GCP update: #4/4

ICH insist that their original text “is still correct” so just adding new text as an addendum results in even more confusion.
“In general there is a need for on-site monitoring before, during, and after the trial: however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.”

Original ICH-GCP 5.18.3

“The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A combination of on-site and centralized monitoring activities may be appropriate.”

Draft Addendum to ICH-GCP 5.18.3
ASSEMBLY
AGENDA PAPERS

9 – 10 November 2016
Osaka, Japan
What’s next in 2017?

Increase number of researchers & organisations supporting MoreTrials.

Write a New-GCP.

Make the campaign a public campaign
EC Clinical Trials Regulation (2014):

“...ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission”
ABOUT MORETRIALS

MoreTrials was created by a number of trialists from leading universities around the world, The James Lind Library, an online library showing the development of fair tests of treatment, and Sense About Science, a charity that helps people to make sense of scientific and medical claims.

See the list of supporters of the MoreTrials Campaign.

The campaign started in January 2016:

Join us.

MORE ABOUT US & JOIN US
The mission of ICH is to “achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.”

Created 25 years ago, its membership reflects its mission to harmonise across regions the regulatory approval process for new drugs developed by industry (text reproduced from ICH’s website FAQs):

“The ICH Parties are comprised of representatives from the following Regulatory Parties:
- USA, the Regulatory Party is the Food and Drug Administration (FDA)
- Canada, the Regulatory Party is the Health Products and Food Branch (HPFB)
- Switzerland, the Regulatory Party is the Swissmedic

As well as from the following Industry Parties:
- Europe, the European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Japan, the Regulatory Party is the Ministry of Health, Labour and Welfare (MHLW)
- USA, the Regulatory Party is the Food and Drug Administration (FDA)
- Canada, the Regulatory Party is the Health Products and Food Branch (HPFB)
- Switzerland, the Regulatory Party is the Swissmedic

or join by emailing me: tim.sprosen@ndph.ox.ac.uk