# Updated open Letter to EMA & ICH: From ~~2~~ 5 research organisations and an international consortium of ~~84~~ 119 health researchers in ~~19~~ 22 countries

***Signatories listed at end:***
***Original signatories of 31st January letter shown in black with***
***new signatories of this letter shown in red***

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.

**Major problems with the proposed revision to the ICH-GCP guideline:** In our view, there are two major problems with the update proposed by ICH:

- **Lack of focus on issues that are most critical for trial quality:** The stated aim of the revised guidance is *"[…] to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity."* It is encouraging that some mention has now been included about principles (such as Quality-by-Design and risk-proportionate monitoring) that can lead to improved trial design and conduct. However, there is still insufficient emphasis on how quality can be improved by focusing attention more on the critical aspects of trial design and conduct (such as the randomisation process, reporting of the most relevant events, maintaining adherence with the study treatment, and achieving completeness of follow-up).

- **Contradictions between the original guideline and the addendum**: ICH's decision not to revise the original text of the ICH-GCP E6 guideline means that there are multiple inconsistencies and contradictions between the original text and the addendum. This is a serious problem because it is very likely to create confusion and uncertainty among those who design, conduct, monitor or inspect clinical trials, as well as to undermine the intended impact of provisions in the addendum for improvement. However, when these contradictions were drawn to the attention of ICH, their written response was that the original text did not require change because it was still "correct".

In support of these concerns, specific examples of the problems with ICH's proposed amendments are indicated on the attached document and the highlighted version of the consultation document. However, as outlined below, the problems with ICH and its GCP guideline are more fundamental.

**Fundamental structural problems with the International Council on Harmonisation (ICH)**

ICH's proposed revision of its E6-GCP guideline raises serious questions about the structure and working of ICH itself. Indeed, its response to concerns about problems with the draft addendum only reinforces widespread concerns that ICH is not fit for the purposes to which it is now being put.

ICH was established in the 1990s by regulatory authorities and the pharmaceutical industry with its stated aim being *"to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for <u>product registration</u>* [our emphasis]*, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines."*

In reality, therefore, its purpose is solely commercial; i.e. to address the desire of industry for mutual recognition of trial data as part of the regulatory review of new drug approvals in different regions. Indeed, ICH is an industry/regulator-focussed organisation that does not involve other relevant stakeholders, such as patient groups and academic researchers involved in non-commercial trials.

Its aim explicitly does not include ensuring the reliable evaluation of the many therapeutic questions that are of public health significance but not of regulatory interest. However, the ICH-GCP guideline is widely applied to such trials, and compliance with ICH-GCP will be required by law in Europe when the EU Regulation on clinical trials is implemented. (Clause 43: *"….the ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation"*).

It is widely documented that implementation of the ICH-GCP guideline has made it more difficult and costly to do clinical trials, distorting the research agenda away from research addressing questions of greatest importance for public health services and patients, and towards trials of new, higher-cost treatments. The adverse impact of the ICH-GCP guideline extends beyond developed countries to resource-poor countries, where ICH has made it particularly difficult to conduct life-saving trials.

Some of the key problems with the ICH organisation are:

- **Failure to address mounting concerns:** Many non-commercial research groups have suggested changes to the ICH-GCP guideline. Indeed, even the pharmaceutical industry (despite being part of the ICH process) has pointed out fundamental problems that have contributed to the crisis in the development of new treatments. However, ICH has ignored these repeated calls for change.

- **Lack of transparency:** Requests for information on any plans to update the ICH-GCP guideline are largely ignored, and the identities of those responsible for producing the latest update are still not publicly available. This lack of openness and transparency prevents constructive dialogue amongst all parties on how the situation can be improved.

- **Lack of engagement with the broader community:** ICH does not include representation from the wider community of academic investigators or funders who have expertise in the design and conduct of clinical trials that address important public health questions. Nor is there evidence of any meaningful involvement of trial participants and the public. By contrast, other groups (most notably the FDA-supported Clinical Trial Transformation Initiative [CTTI]), have demonstrated the value of taking account of the perspectives of all those involved in the clinical trial enterprise (including not just industry and regulators but also academic investigators, trial participants and the wider public) in the development of clinical trial guidance and its interpretation.

**A better way forward**

It is not appropriate to leave the future development of GCP guidelines for clinical trials to a group representing industry and regulatory authorities only that is focussed solely on the registration of new drugs. Instead, a new GCP guideline should be developed that is firmly founded on those key principles that really matter to trial quality (i.e. have a meaningful impact on the rights, safety and wellbeing of trial participants and on the reliability of the results for the subsequent treatment of future patients) and that is relevant for different types of clinical trial. This new guideline should be developed in an open and transparent process that involves everybody interested in clinical trials.

If you have questions or would like to discuss anything, our contact is tim.sprosen@ndph.ox.ac.uk

**Signed by the following research organisations:**

**Professor Francoise Meunier**
Director Special Projects, EORTC
*(signed on behalf of)*

**European Organisation for Research and Treatment of Cancer (EORTC)**

http://www.eortc.org/

**Professor Fausto Pinto**
President, ESC
*(signed on behalf of)*

***European Society of Cardiology (ESC)***

https://www.escardio.org/

**Professor Colm O'Morain**
President, ABRE
*(signed on behalf of)*

**Alliance for Biomedical Research in Europe (ABRE)**

http://www.biomedeurope.org/

**Dr Sarah Clarke**
**President, BCS**
*(signed on behalf of)*

***British Cardiovascular Society (BCS)***

http://www.bcs.com/pages/default.asp

**Professor Kate Leslie**
**ANZCA Clinical Trials Network Chair**
*(signed on behalf of)*

**Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trials Network**

**ANZCA Clinical Trials Network**

http://www.med.monash.edu.au/sphpm/anzca/

**Signed by an international consortium of health researchers with experience in design, conduct, analysis and interpretation of clinical trials of public health questions (alphabetically by country):**

**Australia:**


**Professor Bruce Neal**
**Professor Anthony Rodgers**
*The George Institute for Global Health*
*University of Sydney*

**Professor John Simes**
**Dr Wendy Hague**
*NHMRC Clinical Trials Centre*
*University of Sydney*

**Professor Paul Glasziou**
*Faculty of Health Sciences & Medicine*
*Bond University*

**Dr Lois Browne**
*Clinical Trials Unit, Cancer Care Centre,*
*St George Hospital, Kogarth, New South Wales*

**Professor Paul Myles**
*Department of Anaesthesia & Perioperative Medicine, Alfred Hospital & Monash University, Melbourne*


**Belgium:**


**Professor Frans Van de Werf**
*Emeritus Professor of Cardiology*
*University of Leuven*

**Dr Raffaella Ravinetto**
*Clinical Trials Unit*
*Institute of Tropical Medicine*
*Antwerpen*

**Dr Marc Buyse**
*IDDI & CluePoints*


**Canada:**


**Professor Salim Yusuf**
**Associate Professor Jackie Bosch**
*Population Health Research Institute*
*McMaster University*

**Professor PJ Devereaux**
**Dr Lawrence Mbuagbaw**
**Dr Toon K Teo**
*Department of Clinical Epidemiology & Biostatistics, McMaster University*

**Professor Joel Lexchin**
*School of Health Policy & Management*
*York University*

**Associate Professor Sanjit Jolly**
*Hamilton Health Sciences*
*McMaster University*

**Professor Dean Fergusson**
*Dept of Medicine, Surgery,*
*& of Epidemiology & Community Medicine*
*University of Ottawa*

**Dr Sadeesh Srinathan**
*Department of Surgery*
*University of Manitoba*

**Professor Marc Rodger**
*Division of Hematology*
*University of Ottawa*

**Professor D George Wyse**
*Emeritus Professor*
*Department of Cardiac Sciences*
*University of Calgary*

**Dr Neill Adhikari**
*Department of Critical Care Medicine*
*University of Toronto*

**Dr Steeve Provencher**
*Pulmonary Hypertension Research Group*
*University of Laval*
*Quebec*

**Dr John Gill**
*Division of Nephrology*
*University of British Columbia*

**Professor Jean-Claude Tardif**
*Research Center, Montreal Health Institute*
*University of Montreal*

**Professor Elijah Dixon**
*General Surgery*
*University of Calgary*

**Dr Marco Tonelli**
*Health Research*
*University of Calgary*

**Associate Professor Alejandro Lazo-Langner**
*Department of Medicine, Oncology,*
*and of Epidemiology & Biostatistics*
*University of Western Ontario*

**Dr Remi Rabasa-Lhoret**
*Platform for Research in Obesity, Metabolism & Diabetes,*
*University of Montreal*

**Professor Jon Barrett**
*Clinical Trial Services Unit*
*University of Toronto*

**Professor Brian Cuthbertson**
*Department of Critical Care Medicine*
*University of Toronto*

**Professor Paul W Armstrong**
*Department of Medicine (Cardiology)*
*University of Alberta*

**Dr Tim Ramsay**
*Ottawa Health Research Institute*
*University of Ottawa*

**China:**

**Professor Lixin Jiang**
*National Centre of Cardiovascular Disease*
*National Clinical Research Centre*
*Fuwai Hospital*

**Croatia:**

**Professor Ana Marusic**
*Department of Research in Biomedicine & Health*
*University of Split*

**Democratic Republic of the Congo:**

**Professor Francine Ntoumi**
*Fondation Congolaise pour la Recherche Médicale*
*University Marien Ngouabi, Brazzaville*

**Denmark:**

**Tarang Sharma**
**Dr Karsten Juhl Jorgensen**
*Nordic Cochrane Centre*
*University of Copenhagen*

**Dr Christian Meyhoff**
*Department of Anaesthesiology*
*Bispebjerg Hospital*
*University of Copenhagen*

**Finland:**

**Professor Elina Hemminki**
*National Institute for Health & Welfare and*
*University of Helsinki*

**Germany:**

**Professor Christoph Wanner**
*Department of Medicine*
*University of Wuerzburg*

**Professor Christoph Hermann-Lingen**
***Department of Psychosomatic Medicine & Psychotherapy***
***University of Goettingen***

**Dr Stefan Schroeder**
*Bayer Healthcare*
*Berlin*

**India:**

**Dr Alben Sigamani**
*Clinical Research*
*Narayana Hrudayalaya Limited*
*Bangalore*

**Italy:**

**Professor Aldo Maggioni**
*Italian Association of Hospital Cardiologists*
*(ANMCO), Florence*

**Dr Luigia Scudeller**
*Clinical Epidemiology Unit*
*IRCCS Policlinico San Matteo Foundation*

**Dr Gianni Tognoni**
*Cardiovascular Research*
*Mario Negri Institute*
*Milan*

**Dr Nino Cartabellotta**
*GIMBE Foundation*
*Bologna*

**Japan:**

**Professor Shinya Goto**
*Research Center of Metabolic Disease*
*Tokai University*

**Kenya:**

**Nicodemus Ivuti Kisengese**
*ClinWin Research Services*
*Nairobi*

**Netherlands:**

**Professor Adam Cohen**
*Clinical Pharmacology, Leiden University Medical Centre and*
*Centre for Human Drug Research*

**Professor Yvo Roos**
*Department of Neurology*
*Academic Medical Center*
*Amsterdam*

**Professor Rick Grobee**
*Institute of Health Sciences & Global Health*
*University Medical Center*
*Utrecht*

**Peru:**

**Professor Hector Garcia**
*Cysticercosis Unit*
*University Peruana Cayetano, Lima*

**Professor Eduardo Gotuzzo**
*Tropical Medicine Institute*
*Peruvian University Cayetano Heredia*
*Lima*

**Poland**

**Professor Andrzej Budaj**
Department of Cardiology
Postgraduate Medical School,
Grochowski Hospital, Warsaw

**Republic of South Africa:**

**Dr Reitze Rodseth**
*Perioperative Research Unit*
*University of KwaZulu-Natal*

**Professor Bruce Biccard**
*Department of Anaesthesia & Perioperative Medicine,*
*University of Cape Town*

**Sweden:**

**Professor Lars Wallentin**
*Uppsala Clinical Research Centre & Department of Medical Sciences*
*Uppsala University*

**Tanzania:**

**Dr Bernard Ngowi**
*East African Consortium for Clinical Research*
*Dar Es Salaam*

**United Arab Emirates:**

**Dr Raghib Ali**
*Public Health Research Center*
*New York University Abu Dhabi*

**United Kingdom:**

**Professor Sir Rory Collins**
**Associate Professor Tim Sprosen**
*Nuffield Department of Population Health*
*University of Oxford*

**Professor Trudie Lang**
**Professor Peter Horby**
**Professor Kevin Marsh**
**Dr Jane Crawley**
*Centre for Tropical Medicine & Global Health*
*University of Oxford*

**Professor Jane Armitage**
**Professor Colin Baigent**
**Professor Martin Landray**
**Associate Professor Louise Bowman**
**Dr Richard Haynes**
*Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford*

**Dr Ben Goldacre**
*Department of Primary Care Health Sciences*
*University of Oxford*

**Associate Professor Ed Juszczak**
*National Perinatal Epidemiology Unit*
*University of Oxford*

**Professor Rury Holman**
**Dr Chris Bray**
*Diabetes Trials Unit*
*University of Oxford*

**Professor Doug Altman**
**Caroline Struthers**
*Centre for Statistics in Medicine*
*University of Oxford*

**Professor Barbara Casadei**
*Radcliffe Department of Medicine*
*University of Oxford*

**Professor Jane Green**
*Cancer Epidemiology Unit*
*University of Oxford*

**Professor Ian Roberts**
*Clinical Trials Unit*
*London School of Hygiene & Tropical Medicine*

**Professor Liam Smeeth**
*Department of Non-Communicable Disease Epidemiology*
*London School of Hygiene & Tropical Medicine*

**Professor Neil Poulter**
*Faculty of Medicine, National Heart & Lung Institute*
*Imperial College London*

**Professor Max Parmar**
**Professor Sarah Meredith**
**Professor Di Gibb**
*MRC Clinical Trials Unit at UCL*
*Institute for Clinical Trials and Methodology*

**Professor Janet Darbyshire**
*Emeritus Professor of Epidemiology*
*University College London*

**Professor Tjeerd van Staa**
*Farr Institute of Health Informatics Research*
*University of Manchester*

**Professor Lelia Duley**
*Nottingham Clinical Trials Unit*
*University of Nottingham*

**Professor David Lalloo**
*Department of Clinical Sciences*
*Liverpool School of Tropical Medicine*

**Professor Elaine McColl**
*Newcastle Clinical Trials Unit*
*University of Newcastle*

**Professor Sir Nicholas Wald**
**Professor Jack Cuzick**
**Professor Graham Macgregor**
*Wolfson Institute of Preventive Medicine*
*Queen Mary University of London*

**Professor Gail Davey**
*Global Health Epidemiology*
*Brighton & Sussex Medical School*

**Professor Shaun Treweek**
*Health Services Research Unit*
*University of Aberdeen*

**Professor Tom McDonald**
*Medicines Monitoring Unit & Hypertension Research Centre*
*University of Dundee*

**Dr Miles Witham**
*School of Medicine*
*University of Dundee*

**Dr Peter Hall**
*Edinburgh Cancer Research Centre*
*University of Edinburgh*

**Professor Keith Fox**
*Emeritus Professor of Cardiology*
*University of Edinburgh*

**Professor David Newby**
*Edinburgh Clinical Research Facility*
*University of Edinburgh*

**Professor Peter Sandercock**
**Professor Rustam Al-Shahi Salman**
**Professor Malcolm Macleod**
*Centre for Clinical Brain Sciences*
*University of Edinburgh*

**Professor Gordon Murray**
*Usher Institute of Population Health Sciences & Informatics, University of Edinburgh*

**Professor Ian Ford**
*Robertson Centre for Biostatistics*
*University of Glasgow*

**Karen Lamb**
*Research Co-ordinator*
*Community Clinical Research Nurses*

**Dr Gill Booth** (*on behalf of)*
*UK Clinical Research Collaboration (UKCRC)*
*Registered Clinical Trial Units Network*

**Dr Andreea Steriu**
*Independent Consultant*
*Public Health & Policy*

**Dr Trish Groves**
*British Medical Journal (BMJ)*

**Professor Usha Menon**
*Gynaecological Cancer Research Centre*
*University College London*

**Daniel Shananan**
*Biomed Central*
*London*

**United States of America:**

**Dr James Neaton**
*School of Public Health*
*University of Minnesota*

**Professor Christopher Granger**
*Duke Clinical Research Institute*
*Duke University*

**Dr Janet Wittes**
*Statistics Collaborative Inc.*

**Professor Robert Harrington**
*Department of Medicine*
*Stanford University*

**Professor Christopher Cannon**
*Harvard Clinical Research Institute*
*Harvard Medical School*
*Harvard University*

**Professor John Alexander**
*Cardiovascular Research*
*Duke Clinical Research Institute*
*Duke University, and*

*Co-chair, Clinical Trial Transformation Initiative (CTTI)*

**Dr Daniel Sessler**
*Department of Outcomes Research*
*Cleveland Clinic*

**Enclosure:** Comments on the Published Update (June 2015) to ICH-GCP: Integrated Addendum to ICH E6(R1):Guideline for Good Clinical Practice E6(R2)

**Summary of comments on the Published Update (June 2015) to ICH-GCP: Integrated Addendum to ICH E6(R1):Guideline for Good Clinical Practice E6(R2)**

**Introduction**

**Page 1:** Whilst there have been some useful inserts to the text, these are exclusively as 'addenda', with no attempt to modify the original text in order to be compatible with (rather than contradict) those inserts, and to ensure an appropriate balance between descriptions of what is proposed in the original text and in the new text. It does not suffice just to insert extra text without amending the other relevant text accordingly. In our view, a much more comprehensive revision of the text is required.

For example, on monitoring, the existing text in section 5.18.3 states "in general there is a need for on-site monitoring, before, during, and after the trial ....in exceptional circumstances ... central monitoring" but then the proposed Addendum on the rest of page 30 is more positive about using central monitoring.

In addition, the existing text in section 5.18.4 (page 31) goes into great detail about what the monitor should do (which is clearly related to site visits), much of which could be done better by a coordinating centre using central monitoring methods (and much of which cannot really be done by site monitors and/or is not a good use of time: see below for specific notes on this section).

By contrast, there is no description of the kinds of things that could be done using central monitoring. It may be that this is not considered to be the place to go into such detail but that should apply both to the detail of site monitoring and of central monitoring (i.e. there is a need to reduce excessive detail in 5.18.4 or make it generic to both approaches).

However, this is just one example of places where proposed inserts require amendment to the existing text in order to achieve the aim outlined in the addendum on page 1.

**Introduction (Addendum), page 1, line 21:** As did the European Commission when it reviewed the impact of the European Clinical Trial Directive, it would be appropriate for ICH to acknowledge explicitly that these increases in complexity and cost have been in large part driven by regulatory guidance (in particular ICH- GCP) and that it is now intended to improve the situation.

**Section 1: Glossary**

**Adverse Drug Reaction, page 2, 1.1 (lines 36-38):** This sentence is internally contradictory: it may not be possible to rule out a causal effect (very difficult to do in individual cases) but there may not be reasonable probability of a causal relationship. Delete the text "i.e." and give some informative guidance on what is a "reasonable probability" (and perhaps what is not).

As a related point, it is not clear that there is evidence to support reporting of so-called "reactions", and there is a strong case for taking a different approach to safety monitoring in randomized controlled trials that would be more appropriate. It is generally accepted that ADR reporting may be useful to pick up big effects on rare outcomes, but that it is not effective for picking up any effects on common outcomes, which is why randomised controlled trials are done in the first place (irrespective of whether the aim is to detect good or bad effects). In that case, should not the use of "reaction" reporting be restricted to just those sorts of effects for which it is most relevant and of health significance (i.e. serious adverse events that would not typically be expected and are thought with a reasonable probability to be due to treatment), and to leave the detection of other effects (good or bad) to the trial to demonstrate when it is completed (or stopped early by the DMC for efficacy or safety reasons)?

**Adverse Event, page 2, 1.2 (lines 44-45):** According to this text, by definition there can be no adverse events in an untreated control group! (Or in a group allocated placebo, which is not really a pharmaceutical product, although technically defined as such.) Without collecting data in the control group, there cannot be an unbiased assessment of causality or even association. Reference to treatment in this definition is not helpful and should be removed. **Lines 47-48:** This text is not needed or helpful, and it causes confusion by referring to a treatment when it is not relevant to whether an adverse event has occurred.

**Coordinating Committee, page 4, 1.18 (lines 112-3):** Most often called a "Steering Committee" so perhaps worth giving as an alternative.

**Essential Documents, page 4, 1.23 (lines 130-133):** The conduct of the study and the quality of the data produced cannot, and should not, be judged from essential documents. Trial quality depends on other trial metrics (eg, study design, completeness of follow-up, treatment adherence etc.) that are not mentioned in this document. The idea that documents alone can suffice in making such judgments is one reason why this document needs a more fundamental re-write.

**Independent Data Monitoring Committee, page 4, 1.25 (lines 139-143):** The IDMC should also consider other relevant information, such as emerging results from other trials with the same or similar drugs.

**Independent Ethics Committee, page 4, 1.27 (lines 149-159):** There is potential for confusion because this Committee is also referred to as an IRB in 1.5.

**Institutional Review Board, page 5, 1.31(lines 174-9):** Why not combine with 1.27 (as is done in 1.25 for DMCs) rather than have separate, but slightly different paragraphs for much the same thing?

**Monitoring, page 6, 1.38 (lines 202-5):** This needs to be revised to state that overseeing the progress of a clinical trial should be done in accordance with the Monitoring Plan.

**Opinion, page 6, 1.42 (line 220):** But not of an IRB? Is this definition needed as there are other "opinions" (eg of regulatory authorities)

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR),page 7, 1.50 (lines 245-54):** In this definition it is unclear whether an SAE and a Serious ADR are equivalent. SAEs may be unrelated to the IMP. The definition of an Adverse Event (see 1.2) specifically allows for an AE to be related or unrelated.

**Sponsor, page 7, 1.53 (lines 267-9):** It would be worth considering explicitly the option of having co-sponsors on trials (as is proposed by the EC Regulation) with the different responsibilities clearly defined in some form of agreement between the co-sponsors. It might also be useful to be explicit that "sponsor" is not the same as "funder".

**Subject/Trial Subject, page 8, 1.57 (line 283):** An individual who does not receive an IMP is still within this definition. It would be preferable to replace the words “as a recipient of” with “because they have been allocated to”.

**Unexpected Adverse Drug Reaction, page 8 (lines 291-6):** Or with the protocol (in case there is additional information that can be included in the protocol that is more specific to the particular study)

**Section 2: The principles of GCP**
**Page 9, 2.9 (lines 336-7):** This is not always possible and it contradicts 3.1.6 and 3.1.7

**Page 10, 2.13 (lines 348-9):** The focus should be on material aspects, not on every aspect.

**Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)**
**Page 12, 3.3.8 (c) (line 440):** It may be useful to refer to Suspected Unexpected Serious Adverse Reactions (SUSARs) here.

**Section 4: Investigator**
**Page 14, 4.3.4 (line 505):** Since the quality of a trial is compromised by losses to follow-up, this document should include a section describing the Investigator’s responsibility to ensure that follow-up is obtained for all patients who are randomized, even if patients have discontinued study treatment. The term “withdrawal” is often incorrectly interpreted by study investigators as meaning that patients stop treatment and do not require any subsequent follow-up, so it would be useful for this document to stress the importance of maintaining follow-up (to the extent possible) in ALL randomized patients.

**Page 17, 4.8.7 (lines 602-7):** This section should mention that its provisions do not apply to emergency situations, and cross-refer to the relevant section (4.8.15).

**Page 19, 4.9.2 (lines 712-3):** What matters is that data recorded on CRFs do not differ from source documents in ways that are important for the reliability of the study results or the safety of the

patients. That is, the focus should be on things that are important and not be distracted by trivial discrepancies. Greater focus in ICH-GCP on what is important is required.

Also, how is it intended to ensure such consistency without doing 100% source document verification, which is very costly and not demonstrated to be of value? Again, focus is required on recommendations that do not inadvertently generate much work and cost while being of debatable value.

**Section 5: Sponsor**

**Page 21, 5.0 (lines 785-834):** These amendments are generally welcome, but they also illustrate the problems with the approach taken to their inclusion. In particular, the addenda sometimes contradict existing text which has not been amended (and needs to be) and/or the level of detail in existing text on relatively unimportant aspects of good clinical trial conduct is excessive by comparison with the detail on important aspects in the addenda. **Line 792:** Here is an example: how does this proportionate approach correspond to section 4.9.2 regarding source document verification? That section (and others) would need to be amended to allow the intent of this addendum to be properly implemented.

**Page 23, 5.2.1 (line 850):** The concept of a co-sponsor arrangement should also be included.

**Page 29, 5.17 (lines 1087-96)**

How useful is it to report single reports to IRBs/IECs in an expedited fashion? Many of them ask what they are supposed to do with such information, which is a fair question. Instead, it would be more sensible for ICH to suggest that it only be done periodically as updated tables. (If IRBs/IECs request such information then it can be provided but that does not require ICH to indicate that it is the right thing to do by including it in their recommendations, even with the caveat of "where required"). Also, there is no mention here of the need for Data Monitoring Committees to be provided with data on adverse drug reactions; since the IDMC is generally unblinded, it is in a better position to make judgements about safety (having due regard to information about efficacy).

**Page 29, 5.18 (line 1101):** Really; why? Again this contradicts the addendum in section 5.0

**Page 30, 5.18.3 (lines 1119-21):** In light of the addendum below (line 1126), this text needs to be modified to conform with the greater emphasis on central monitoring. Also, it contradicts the highlighted text in the first para of the addendum.

**Page 31, 5.18.4 (lines 1149-1217):** The detail in this section is excessive by contrast with the detail about how central monitoring is done. It should be reduced and focus on principles and things that really matter. Moreover, some aspects of what is suggested be done by a site monitor would be better done by central monitoring (e.g. (a), (b), (i), (j), (l), (m) and (o)) or that cannot really be done by site monitoring or are not important/critical.

**Line 1153:** No, this is better done by the coordinating centre.

**Line 1159:** Excessive detail.

**Line 1171:** Or should this be the investigator's trial staff?

**Line 1173:** How can this really be done: ie how does a monitor determine that consent was properly "informed" for each participant without sitting in during each interview? This is an example of making recommendations without thinking through the implications.
**Line 1184:** No, this is better done by the coordinating centre.
**Line 1186:** No, contradicts addenda about doing things in a proportionate manner with a focus on things that matter for the trial.
**Line 1188:** Better done centrally.
**Line 1195:** That would require 100% checks, which is not consistent with the more proportionate approach proposed in the addenda.
**Line 1196:** What if not relevant? This illustrates the problem of excessive detail rather than general principles.
**Line 1200:** Better done centrally.
**Line 1205:** Focus should be on errors in key measures (e.g. primary outcomes) and not on "any" errors (e.g. in secondary data).
**Line 1210:** Better done centrally.

**Page 33, 5.19.1 (line 1254):** In ways that are importantly relevant to the reliability of the results and safety of the patients, and so avoid undue focus on trivial discrepancies.

**Page 34, 5.20.1 (line 1279):** Significant noncompliance, to be consistent with the addendum below. This is yet another illustration of the need to modify the existing text rather than just drop in addenda while leaving the existing text unchanged.

**Page 34, 5.21 (lines 1292-7):** Delete as it is already in 4.12.

**Page 34, 5.22 (lines 1298-1305):** Move to replace 4.13 (and so avoid unnecessary replication and risk of contradiction)

**Page 35, 5.23.1 (line 1308):** No; focus should be on ways that are relevant to reliability of results or safety of patients (and so be consistent with the addenda).

**Page 35, 5.23.5 (line 1319):** Why; surely the aim should be to have good communication of the sponsor and/or CRO with the investigators rather than between the separate investigators?-

**Section 6: Clinical Trial Protocol and Protocol Amendments**
This section should come before all of the sections on reporting and monitoring since the design comes first and, in particular, the quality-by-design (as espoused in the addendum 5.0) then leads to improved conduct.

**Page 36, 6.4.3 (line 1362):** Randomisation/blinding is one of the most critical aspects of the design of a trial, and yet there is no detail of what matters, by comparison with all of the detail given (2 full pages) on site monitoring in section 5.18.4.

If the counter-argument is that such detail for randomization is provided in a separate document then the same argument should be made for the excessive detail on site monitoring which should be removed and more balanced text on central and site monitoring provided.

There is nothing on the importance of follow-up of patients who stop taking their study treatment so that unbiased intention-to-treat analyses can be conducted. The failure of ICH-GCP to cover this point has been documented to have resulted in ICH-GCP-trained staff believing that such follow-up for ITT analyses is not important.