



Risk proportionate approaches in clinical trials – August 2016

Joint response from Cancer Research UK and the British Heart Foundation

It is vital that the rules and regulations for clinical research always support patient safety, address ethical concerns and ensure scientific validity. However, unnecessary or inflexible regulations create significant extra costs in running clinical research for funders. We therefore welcome the opportunity to respond to this consultation on what we perceive to be an issue of vital importance.

The European Clinical Trials Regulation (CTR) recognises that many clinical trials pose only a minimal additional risk to subject safety compared to normal clinical practice. The clinical researchers we spoke to found it very encouraging that a risk proportionate approach to conducting trials is being implemented and we welcome the opportunity to respond to this consultation.

General comments:

Risk adaption

We welcome that the recommendations make it clear that risk adaptation in the conduct of a trial (using a proportionate approach) may apply in any clinical trial (i.e not only 'low intervention' trials). In the past many of the requirements for monitoring, applications and reporting were set at a level much stricter than was necessary for most non-commercial research using treatments that are well understood and therefore pose a lower risk to patients on trials.

Clinical Study reports

As stated in ICH E6 (Good Clinical Practice), not all Clinical Study Reports will be to ICH E3, unless they are part of marketing authorisation. Furthermore ICH E3 is a guideline, not a rigid set of requirements or a template. It is essential that this is acknowledged in the risk adaptation guidance.

Readability

The language used in the guidance is at times too similar to the legal writing style used in the Regulation and is difficult to understand. Since this guidance document is designed to make the regulation easier to understand, and ensure consistent interpretation by different member states, it would benefit from use of some of the principles described in the 'Summary of clinical trial results for laypersons' guidance.

Comments relating to specific lines:

Line 76

We would suggest changing 'academic' to 'non-commercial' or 'non-commercial/academic'. Whilst the term 'non-commercial' captures the academic sphere of clinical trials, 'academic' does not completely encompass all non-commercial trials.

Lines 78-80

Sentence refers to clinical trials with IMPs intend to be included in an application for a marketing authorisation and clinical trials with novel IMPs. In most cases these are the same. Therefore we suggest that instead of simply referring to 'novel IMPs' in this instance, the guidance specifies: 'clinical trials of novel IMPs where an application for a marketing authorisation is not expected'.

Line 80

We would suggest that the word 'only' should be deleted



Lines 93-94

We would advise changing these lines to:

...(as defined in Article 2(3) of the Regulation - "low intervention clinical trials")...

Line 105

Grammatical recommendation: 'be also' should be changed to 'also be'

Lines 178-180

For clarity, we would advise changing this to read:

The risk evaluation process covers the assessment of:

- the likelihood of potential hazards (identified risks) associated with the trial
- the impact-of these hazards, if they were to occur, on subjects' safety and on data integrity
- the extent to which such hazards would be detectable

Line 183

Grammatical recommendation: The first word should be 'Risk', or if left as 'Risks' then the first 'its' in the sentence should be changed to 'their' and second 'its' should be deleted

Lines 189-190

The guidance states that risk evaluation should commence prior to finalisation of the protocol as it may influence financing. We support starting the risk evaluation at this stage, but it should not need to be finalised prior to completion of the protocol, as additional protocol changes may be required at a later stage. This would benefit from clarification.

For consistency, the line should read: Risk identification and evaluation should commence

Line 192

This line should read: Following risk identification and evaluation in a trial,

Line 194

For clarity these lines should read: The documentation should include the rationale for any specific actions required and identify those responsible for them (e.g. monitor, investigator etc.)

Line 196

For consistency these lines should read: ...as part of the risk assessment and risk mitigation of...

Line 203-204

These lines should read: Examples of risk assessments, and guidance on performing them, are available on the websites of some national authorities and academic and other non-commercial sponsors, as part of these organisations' initiatives.

Lines 206-208

For clarity these lines should read: The purpose of risk control is to determine whether the risk is acceptable, and if not to reduce the risk to an acceptable level.



Lines 211-216

This is a long sentence so should be bulleted to aid clarity:

Risk assessment and risk mitigation would typically involve a variety of functions, and therefore may include various personnel such as:

- data managers, statisticians, trial managers, monitors and/or auditors
- personnel who have more direct involvement with patients such as clinical experts
- investigators with an understanding of the therapeutic area and use of the proposed IMP
- pharmacists and research nurses

Line 267

Grammar recommendation: this should read 'are scarce'.

320-323

Grammar recommendation (Insert paragraph break, and slight rewording for clarity):

'The rules for safety reporting from the investigator to the sponsor should be described in detail in the protocol.'

The risk assessment and mitigation plan may also identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and require expedited reporting from the investigator to the sponsor. These requirements should be included in the protocol.'

Lines 345-350

The meaning of this sentence is unclear.

Lines 373-378

Suggest bulleting the list of examples

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Cancer Research UK

Cancer Research UK's vision is to bring forward the day when all cancers are cured. Over the last 40 years, cancer survival rates in the UK have doubled. In the 1970s just a quarter of people survived. Today that figure is half. Our ambition is to accelerate progress and see three-quarters of patients surviving the disease within the next 20 years.

Every year more than 25,000 people take part in one or more of over 250 clinical trials supported by the charity.

Every year more than 25,000 people take part in one or more of over 250 clinical trials supported by the charity. In 2015/16, Cancer Research UK spent £432 million on research across the UK, including our £28 million contribution to the Francis Crick Institute. CRUK directly funds over 200 clinical trials. More than a quarter (28%) of these trials involve at least one other EU country. One in three (33%) of CRUK-supported clinical trials have involvement from countries outside of the UK.

British Heart Foundation

The BHF is the UK's leading heart charity. We are working to achieve our vision of a world in which people do not die prematurely or suffer from cardiovascular disease. Thanks to modern treatments built on our research, huge progress has been made in saving lives. Most babies born today with heart defects survive and seven out of ten people survive a heart attack. However, heart and circulatory disease still kills one in four people and affects 7 million people in the UK, so there is so much more to do.

The BHF is the largest independent funder of cardiovascular research and the third largest charitable funder of medical research in the UK. Each year, thanks to the generosity of our supporters, we are able to fund around £100 million of new research across the UK, in all four nations. Our funding portfolio extends from laboratory science to clinical trials and population studies. We fund people from PhDs to professors as well as investing in large programme and project grants.