General Feedback on Guidance

Here we would like to hear any general feedback you have on the guidance. In particular, whether the guidance fulfils our original objectives that it would be: 1. Based on key scientific and ethical principles, and focused on issues that materially matter to and influence the well-being of trial participants and the reliability of RCT results 2. Clear, concise, consistent and proportionate to the context and setting in which RCTs are being conducted, recognising that there are risks associated with both usual clinical practice and a lack of reliable evidence on intervention effects 3. Forward looking, fostering innovation in health interventions and trial methods, including the appropriate use of routine healthcare data, technologies, and designs 4. Flexible, widely-applicable, utilisable & durable, across disease areas, intervention types, development phases, trial designs, geographies and time.

Does the guidance successfully fulfil objective 1?

Objective 1: The guidance will be based on key scientific and ethical principles, and focused on issues that materially matter to and influence the well-being of trial participants and the reliability of RCT results

FPM Response: Agree

Comments box:

FPM generally agrees that the guidance fulfils objective 1, however some items might be usefully added including:

Reference to the ICH principles of Good Clinical Practice (particularly important if data from the study is intended to support regulatory approval of a novel therapeutic/diagnostic/device),

Expand on the principles of informed consent not least by reassuring research subjects of the voluntary nature of trial participation, that a decision not to participate will not impact the patients care at the institution and that the subject may withdraw from the trial at any time without penalty.

Expand on the principles of consent in special circumstances (research in children and other vulnerable populations eg unconscious/incapacitated subjects, diminished mental competence etc)

Reporting of trial findings in the peer reviewed literature at the earliest opportunity following trial completion.

Does the guidance successfully fulfil objective 2?

Objective 2: The guidance will be clear, concise, consistent and proportionate to the context and setting in which RCTs are being conducted, recognising that there are risks associated with both usual clinical practice and a lack of reliable evidence on intervention effects.

FPM Response: Neutral

FPM Comment: Suggest adding a forward to Item one to include comment that the decision to conduct a clinical trial should be taken after establishing the extent of the current state of knowledge – repeating work already done has limited scientific value – and emphasize the importance of providing a rationale for the study including the relevance of the trial design (type of trial, patient population included etc) and the (anticipated) relevance of the outcome for medical practice.

Does the guidance successfully fulfil Objective 3?

Objective three: The guidance will be forward looking, fostering innovation in health interventions and trial methods, including the appropriate use of routine healthcare data, technologies, and designs

FPM Response: Disagree

FPM Comment: The COVID pandemic has seen a range of novel approaches to the management of clinical trials, not least direct patient recruitment particularly into trials recruiting patients within a community setting, digital/witnessed consent procedures and indirect monitoring of trial data accrual (‘remote’ monitoring). Reference to these additional trial procedures might assist innovation in trial methods. In addition, for some interventions routine healthcare might require adjustment dependent on the patient population recruited, the nature of the agent/device/diagnostic under investigation and the outcomes of interest: thus there may be a need to consider what data can be accrued from a digitised healthcare record and what additional information might be required to meet the trial objectives. This data should also be made available to the subjects healthcare record.

Does the guidance successfully fulfil Objective 4?

Objective 4: The guidance will be flexible, widely-applicable, utilisable & durable, across disease areas, intervention types, development phases, trial designs, geographies and time.

FPM response: Neutral

FPM comment: There is a need to ensure independent ethical review of the planned research and appropriateness of the consent procedures as well as regulatory authority review/approval for investigational medicinal products/diagnostics/devices. Some cross reference to relevant regulatory procedures may be helpful.

Specific feedback on Principles and Guidance

We welcome feedback on specific principles and sections of the guidance. In particular, we would appreciate comments focused on the following:

> Are there aspects that need strengthening?
> Are there aspects that need more emphasis?
> Are there important omissions? Is something missing?
> Is there unnecessary duplication or repetition?
> Could the clarity be improved?

**For ease of reference, the 7 key principles underpinning the guidance are below:**
1) Good RCTs are designed to produce scientifically sound answers to relevant questions
2) Good RCTs respect the rights and well being of participants
3) Good RCTs are collaborative and transparent
4) Good RCTs are designed to be feasible for their context
5) Good RCTs manage quality effectively and efficiently
6) Good RCTs have appropriate trial governance
7) Good RCTs use a proportionate approach to clinical safety

Would you like to share feedback on specific principles?

Yes/No if Yes comment on the relevant principle

Principle 1

*Appropriate trial population*: FPM suggests adding a comment concerning the importance of preplanned analyses of important subgroups (eg age, gender, other comorobidities etc) and accommodating this by ensuring appropriate randomization procedures for factors which may impact the trial outcome

*Relevant Outcomes:* FPM suggests adding a comment that trial outcomes should be sufficiently specific and relevant to longer term outcomes where appropriate

*Proportionate, efficient and reliable capture of data:* FPM suggests emphasis to be placed on ensuring that sufficient demographic data is collected to permit relevant subgroup analyses and the importance of collecting information relevant to the assessment of subject safety. We suggest that the importance of data standards to ensuring data quality might be more greatly emphasized eg by a short discussion in a specific paragraph.

*Adequate RCT size*: FPM suggests qualifying the statement ‘statistically powered’ eg prospectively statistically powered for the primary outcome using an appropriately selected statistical test.

*Adherence to allocated trial intervention*: FPM suggests that trial procedures should be adequate to prospectively monitor adherence to trial intervention so that steps can be taken to understand the reasons for non adherence with a view to facilitate adherence where this is poor (NB some interventions might of their nature be associated with poor adherence for many reasons and while it may be possible to facilitate adherence in a clinical trial, the methods required might not be as successful in a clinical practice setting)

*Monitoring emerging data on safety and efficacy*: This paragraph should open with a clear statement that safety data (particularly important adverse experience) should be regularly reviewed and shared in with the trial site investigators. This is because the trial site investigators are the people managing safety of participants day to day and they must be made aware of serious adverse events which occur at other sites, and the outcome of any intervention, to ensure they can manage trial subject safety appropriately. While an independent data monitoring committee can be helpful in regularly assessing the trial data (and can be unblinded where appropriate) these reviews may be too late to prevent significant safety concerns emerging without vigilance at site level.

 Principle 2

*Relevant consent*: Some important items are missing in this paragraph including statements reassuring research subjects of the voluntary nature of trial participation, that a decision not to participate will not impact the patients care at the institution and that the subject may withdraw from the trial at any time without penalty.

Principle 3

It is suggested that this may be the point to add comment concerning the relevance of the research, that is adding to knowledge and not repeating investigations already completed.

 Principle 6

It is suggested that this section be expanded to include the principles of independent ethical review of the protocol and informed consent processes, the need for regulatory authority review of studies with investigational medicines (IMPs)/diagnostics/devices and appropriate quality assurance measures for IMPs at the point of manufacture/release/dispensing.

Principle 7

*Evaluating and responding to potential external safety signals:* This section only considers trial amendments related to safety, but all amendments to the trial protocol should be submitted to ethical review, whether safety related or not.

Practical Application of the Guidance

In this section, we want to learn more about how best we can support you in practically applying this guidance to your work.

11. Please select the resources that would be most helpful and beneficial for you to apply the guidance to your work.

Most helpful

Moderately helpful

Least helpful

Supplementary document with examples

Explanatory videos

Training materials

Diagrams and visual illustrations

Website with interactive guidance

Other suggestions for additional resources

FPM suggests drawing the attention of the trialist to existing guidelines on trial conduct and quality assurance, particularly the work of the ICH most notably the ICH Efficacy Guidelines <https://www.ich.org/page/efficacy-guidelines> which emphasize the common principles cited in this document.