

Medicines and Healthcare products Regulatory Agency Consultation on proposals for legislative changes for clinical trials 14 March 2022

Patient and public involvement

1. Do you agree that the legislation should include a requirement for the involvement of people with relevant lived experience in the design, management, conduct and dissemination of a trial?

Yes. This should be a priority. As well as gaining a wealth of knowledge from patients about their condition, engagement shows respect for patients. Coproduction of trials is very important and must be legislated for to ensure it happens in reality. This must not be a tokenistic step but an essential part of the process where adequate resources and time are invested. Any coproduction processes must prioritise inclusivity and consider underrepresented people/groups, such as ethnic minorities, pregnant or breastfeeding people.

Research transparency

2. Do you agree that the legislation should include a requirement to register a trial?

Yes. Trials should be registered with the EU Clinical Trials Registry. Research should be as open and transparent as possible. We recognise, however, that some groups prefer to register with clinicaltrials.gov (a privately and publicly funded database of clinical trials conducted around the world). We suggest that there should be a link between the EU clinical trial registration and clinicaltrials.gov.

3. Do you agree that the legislation should include a requirement to publish a summary of results within 12 months of the end of the trial unless a deferral has been agreed?

Yes. Doctors need accurate and unbiased information on the efficacy and safety of different treatments to help them prescribe properly, safely and most effectively for their patients. If data from clinical trials are withheld or otherwise not available, doctors cannot be sure of the risks and benefits of using particular drugs thus risking avoidable harm to patients and wasting scarce NHS resources.

Under-reporting betrays the altruism of research subjects, who participate in clinical trials in the expectation that the risks they undertake will help to advance medical science and benefit society. Where results go unreported there is a risk that research will be repeated unnecessarily, wasting the resources of research funders, many of which are charities, and the time and efforts of researchers and volunteers. Access to full clinical trial information also allows researchers to identify and investigate specific questions of importance and to improve study designs to achieve better results, which in turn benefits patients.

Nonetheless, we recognise that for large trials with prolonged analysis stages, 12 months could be a challenge and would suggest that an extension to 18 months could be offered if required. The reasons for any deferral should be published.

We also recognise that there will be a need to ensure that journals are incentivised to publish neutral or negative results. Having said that, results do not necessarily need to be published in a peer-reviewed journal and, if necessary, pharmaceutical companies and other funders should publish the results themselves.

4. Do you agree that the legislation should include a requirement to share trial findings with participants? (or explain why this is not appropriate)

Yes. Medical and other health care research is essential for the development of the knowledge base and the treatment options needed to provide optimal care for all patients. The UK has a strong track record in conducting medical and health care research and we want it to continue to stay that way, but this means that we need patients and the public to be confident of the benefits of participating in clinical research, including being open about the results from trials with those that volunteer to participate in them. If some data continue to be withheld it may become more difficult to recruit the volunteers we need for such essential research in the future.

The same applies to any carers and guardians of trial participants as appropriate. There should also be a requirement that trial findings are presented in a way that participants can understand and that the sharing of findings is done in a timely manner.

Clinical trial approval processes

5. Do you support a combined MHRA and ethics review, with an initial decision given on the application (i.e. approval or a request for further information) within a maximum timeline of 30 days from validation?

To maintain public confidence in the ethics review process, we believe that this should be kept separate from the MHRA review. Public confidence in the process is more important than speed. It is vital that this is robust and of the highest ethical and regulatory standard.

We do however recognise that timing is important as study start up time is an important factor in determining whether studies come to the UK. Additionally, the COVID-19 pandemic has highlighted the benefit of fast paced research and rapid outcomes and improvements. Hence, we agree that it would be a positive development if we were able to get both MHRA and ethics review completed within the specified timeframe. It might however be better to express the deadline in terms of working days to account for times of the year when there are a number of public holidays.

6. Do you support a sponsor-driven timeline to respond to any requests for further information (nominally 60 days but with flexible extension)?

Yes

7. Do you support a combined MHRA and ethics final decision on a trial of a maximum of 10 days, following receipt of any Requests for Further Information (RFI) responses? The overall time for a final decision would be sponsor driven, depending on their need to take an extended time to respond to an RFI.

Yes. This is a reasonable timeline based on the assumption that sponsors would provide the further information requested in a format or manner that facilitates speedy decision-making.

8. Do you support the ability for the regulators to extend the timeframe for medicinal products or trials where the risks involved may be greater so that independent expert advice can be sought?

Yes. Although, there must be clear guidance for when and how regulators make such decisions.

9. Do you consider it appropriate that a clinical trial approval should lapse after a specified time limit if no participants have been recruited?

Yes. However, we would be open to a lengthy time limit as changing economic circumstances may affect the viability of certain proposed trials and it may be sensible for companies or sponsors to delay undertaking them. Events such as the COVID-19 pandemic for example could and have delayed the undertaking of clinical trials by at least two years. We would also be open to allowing for exemptions if a good rationale was provided.

10. Do you agree that the detail currently outlined in schedule 3 would be better in the form of guidance rather than legislation?

Yes. This would allow for a more agile and flexible process.

11. Do you consider that a trial sponsor having sight of Requests for Further Information (RFI) when they are ready, rather than issued when the final part of the assessment is complete would be advantageous?

Yes. However, there should be consideration for how this would impact the proposed timetable.

12. Do you consider that the ability to receive an RFI during the review of a substantial amendment would be beneficial?

Yes.

13. Do you agree that we introduce the concept of a notification scheme into legislation?

Yes. Although this would depend on the specific details of the notification scheme in the final proposals.

14. Do you consider that the proposed provisions for clinical trial approvals strike the right balance of streamlined, proportionate approval with robust regulatory and ethical oversight?

Yes, with the amendments we are proposing in this response. There should also be consideration given to the proposals with regard to their compatibility with EU legislation to ease collaborative working between the UK and the EU.

Research ethics review

15. Do you have any views about the membership or constitution of Research Ethics Committees?

The membership must be diverse and be both representative of the patient group affected (or their carers as appropriate and is practical) and include relevant specialists in the specific field of study.

16. Should we introduce legislative requirements to support diversity in clinical trial populations?

Yes. This is important to enrich the study population and generate more meaningful data for the wider population. It is important to note that disease type may affect specific groups of people and diversity groupings may influence trial outcomes. There may be occasions where there is a clinical

reason for focusing the research on a particular group (e.g. sickle cell anaemia). Diversity groupings should be fully documented.

We would also suggest the added complexity and costs of this best practice should be recognised. For example, more time might need to be provided to recruit sufficient participants from so called 'hard to reach' groups, and investment would need to be made in translation services.

Informed consent in cluster trials

17. Do you agree that legislation should enable flexibility on consent provisions where the trial is considered to have lower risk?

We agree that in principle, a proportionate or flexible approach to obtaining informed consent may be appropriate for low-risk trials and has the potential benefits, however we would need to see the details of the proposed legislative changes, which are not clear in the consultation document, before providing a definitive answer. Overall, any changes under consideration must safeguard the informed consent of the participant and ongoing public trust in medical research.

18. Do you agree that it would be appropriate for cluster trials comparing existing treatments to use a simplified means of seeking agreement from participants?

We appreciate the logic of simplifying agreement for trials in treatments that have already been approved. However, consideration would need to be made for how similar to the original approval new usage is going to be. Additionally, the extent and by what means it will be simplified must be clarified.

Central to any approach must be safeguarding the interests of the patient or participant and his or her informed consent to participation. It is imperative that the desire to simplify or streamline the informed consent process does not take, or is not perceived to take, precedence over this important consideration. Simplifying procedures must not equate to undermining or weakening the ethical importance of the consent process. Although simplicity, efficiency and proportionality are important considerations, these should not come at the expense of the standard of care owed to patients or research participants and the rights of patients to participate in trials of their own free will.

Proceeding with research without the level of consent expected by patients risks endangering trust in NHS research and the health service in general, which would far outweigh the benefits that could result from the research going ahead. The balance of proportionality regarding the level of information that needs to be provided and the format in which it is given needs to be carefully considered to ensure that it meets the needs and expectations of patients so that doctors who obtain patients' consent can be assured, in line with General Medical Council (GMC) guidance, that patients have given their informed consent to participate in a trial.

Particular caution is needed if trial recruitment will involve patients who lack the capacity to consent to participation. Where the process of seeking consent does not differ significantly from current best practice, and is sufficient to enable a proxy decision maker to consent on behalf of the research participant, proportionate or streamlined means of seeking consent could be used in trials involving patients who lack the capacity to consent themselves. The introduction of measures to simplify the consent process should not weaken or be perceived to weaken the safeguards for these vulnerable patients.

Where data is needed from the medical records of those participating in the trial, the process of seeking consent must include consent for such information sharing.

Safety reporting

19. Do you agree to remove the requirement for individual SUSARs to be reported to all investigators? They will still be informed via Investigator's Brochure updates.

No. It is important that Suspected Unexpected Serious Adverse Reaction (SUSARs) are monitored and reported. However, we recognise that a more flexible way of informing the investigators with better justification could be developed.

20. Do you agree with removing the requirement to report SUSARs and annual safety reports to RECs? Noting that MHRA will still receive these and liaise with the REC as necessary.

No. The Research Ethics Committees still need to see these.

21. Do you agree that, where justified and approved by the regulatory authority, SUSARs can be reported in an aggregate manner?

Where the same or similar adverse events occur, reporting them in an aggregate manner may be beneficial for analysis purposes. However, separate incidents should be reported separately. Aggregating unrelated incidents may cause delays in reporting.

22. Do you agree with the proposal to remove the requirement to include listings of serious adverse events and serious adverse reactions in annual safety reports and instead include an appropriate discussion of signals/risks associated with the use of the medicinal product as well as proposed mitigation actions?

No. The proposal lacks transparency and risks undermining the confidence of the public.

23. Do you agree with the proposal to extend the written notification for Urgent Safety Measures from no later than 3 days from when the measure was taken, to no later than 7 days?

No. We do not see adequate rationale or justification in the proposal for extending this deadline.

24. Do you agree that the proposed safety reporting requirements will reduce burden on researchers but maintain necessary levels of safety oversight?

No. We are concerned that, without the amendments we are suggesting in this response or points of clarification, some elements of the proposals fail to prioritise patient safety, public confidence and research transparency. We are also concerned that in an attempt to reduce the burden on researchers the proposals could undermine confidence in the system and therefore risk the UK's strong standing in medical and health service research and the extent to which procedures in the United Kingdom will align with and be recognised by the European Union. The proposals may also inhibit the opportunities for joint working with colleagues in the EU.

Good clinical practice

25. We are proposing changing the current legislation to incorporate more elements on risk proportionality. Our desire is that this will facilitate a culture of trial conduct that is proportionate and 'fit for purpose' for both researchers and regulators. Do you agree with this approach?

Greater clarity is needed on how risk is to be determined and by who before coming to a definitive view on this. As mentioned above, we would be concerned by any proposals that undermined patient safety or public confidence in the system.

While the question refers to risk proportionality being 'fit for purpose' for researchers and regulators, it does not reference patients or participants whose interests must be central to any decisions made.

26. Do you agree that service providers of electronic systems that may impact on participant safety or reliability of results should also be required to follow the principles of GCP?

Yes. We believe that machine learning must not be exempt from the principles of Good Clinical Practice. With an increase in use of electronic systems in all aspects of trial conduct, it is especially important that this is explicitly stated.

27. Do you agree that the current GCP principles require updating to incorporate risk proportionality?

As mentioned in question 25, we believe more detail is needed around determining risk and proportionality. We agree that if changes were made, GCP should be updated as appropriate.

28. What GCP principles do you consider are important to include or remove and why?

We must maintain the broad principles of GCP to protect the rights and well-being of trial participants and the reliability of the trial results. There may be an opportunity to improve GCP principles rather than just include or remove some of them.

Sanctions and corrective measures

29. Do you agree that regulators should be permitted to take into account information on serious and ongoing non-compliance that would impact participant safety they hold when considering an application for a new study?

Yes. Patient safety is paramount so the regulator should have access to relevant information where the non-compliance is serious, ongoing, or likely to affect patient safety. The circumstances where this is applicable must be clearly defined.

30. Do you agree it would be appropriate to enable regulatory action to be taken against specific part of a trial rather than the trial as a whole?

Yes.

Manufacturing and assembly

31. Do you agree that we should introduce the term 'non-investigational medicinal product' into legislation to provide assurance on the quality and safety of these products?

Yes. If studies are being conducted on non-investigational products, then the term should be introduced.

32. Do you agree that where a medicine is labelled according to its marketing authorisation (and is used in its approved packaging) that specific clinical trial labelling may not be required?

Yes. However, this should only apply if the medicine is being used for its licence indications. If the medicine is being trialled for something completely different, then it must be labelled in accordance with the trial protocol. If a placebo is being used it cannot be used with original labelling and the non-placebo arm would need to be similarly labelled.

33. Do you agree that it is appropriate for radio pharmaceuticals used in a trial to be able to be exempted from the need to hold a Manufacturers Authorisation for IMPs?

No. Authorisation must be detailed in full prior to getting trial approval.

Definitions and other terminologies

34. Do you have any comments or concerns with the proposed updates to the definitions outlined?

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35. Which healthcare professionals do you consider should be able to act as an Investigator in a trial?

Healthcare professionals that have received the appropriate training in Good Clinical Practice and clinical trials and are appropriately regulated.

36. Do you consider that the legislation should state that any appropriately trained and qualified member of the investigator's team can seek consent?

Yes. However, there must be clarity and detail on what constitutes appropriately trained and qualified. The trial protocol must state clearly who, why, and how consent will be obtained.

37. Do you consider it appropriate that data collection following MHRA approval for use of an unlicensed medicine can be considered as non-interventional where the collection is according to the 'approved' use?

We agree in principle as long as there is no compromise in the quality and rigour of the process. The responsibility lies with the trial and the investigators. Marketing authorisation should not alter the trial protocol and this should not change during the trial.

Conclusion

38. Do you agree that the proposed changes introduce improvements to streamline processes and to remove unnecessary burdens to trial sponsors?

Some elements of the proposals have the potential to streamline processes. Patient safety, transparency and robust approaches must remain central to any proposals. However, sponsorship

processes should not duplicate other elements of trial design or governance which can cause unnecessarily bureaucracy and can delay ground-breaking fast-paced research and rapid outcomes.

39. Are there other aspects of the Clinical Trials legislation that you believe have not been considered but need to be? For example, is there something you think should be addressed now or should be considered for future legislative changes?

- How the proposed changes will specifically affect research with children, young people & vulnerable people
- How current proposals align with EU regulations and how this will impact collaborative cross-border research (for example the impact on the research of rare diseases)
- The potential advances in health technology and how this will fit into current legislation

40. Are there potential costs or financial implications of the proposals outlined that you think we need to especially consider?

Patient safety, representation, transparency and public confidence must be at the centre of trial design but the practical steps to incorporate these elements often comes at an increased cost. For example, recruiting a more diverse trial population may involve engaging with marginalised groups who may not speak English, have access to online services or be in regular contact with healthcare services. The use of a translator and efforts to engage with or hard to reach participants is costly and time-consuming. We must ensure that researchers hold these core principles at the centre of there research through robust clinical trial legislation and guidance, but this must be supported by we well-funded and resources ecosystem in the UK. This should be considered in the Government's independent review into ethnic inequalities for medical devices.