CONSULTATION ON PROPOSALS FOR LEGISLATIVE CHANGES FOR CLINICAL TRIALS

Better regulation, for better trials, for better health

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1. Executive summary

The Medicines and Medical Devices Act 2021 provides the powers to update the legislation for clinical trials. This brings the opportunity, having left the European Union, to design a world-class sovereign regulatory environment for clinical trials that will support the development of innovative medicines and ensure that the UK retains and grows its reputation as world leading base for life sciences, generating opportunities for skilled jobs in the UK. This consultation outlines a set of proposals, capitalising on this opportunity, to reframe the UK legislation for clinical trials, responding to the needs of the sector to deliver a more streamlined and flexible regulatory regime, whilst protecting the interests of patients and trial participants.

This consultation specifically relates to clinical trials and the medicinal products used in clinical trials (Investigational Medicinal Products, 'IMPs'). These proposals are to update the current UK legislation that governs clinical trials, The Medicines for Human Use (Clinical Trials) Regulations 2004" (SI 2004/1031), as amended, which transposes the EU Clinical Trials Directive 2001/20 EC into UK law.

Through the legislative proposals in this consultation, we aim to enable a thriving clinical research environment in the UK, reflecting innovative trial design and delivery and supporting the wider programme of work being taken forward as part of the UK vision for the future of clinical research delivery in Saving and Improving Lives: The Future of UK Clinical Research Delivery and its implementation as well as the Life Sciences Vision. These proposals also take steps to remove bureaucracy to support an efficient and effective clinical trials environment, in line with recommendations from the Taskforce for Innovation, Growth and Regulatory Reform (TIGRR) and support faster access to new, innovative treatments for patients.

We are seeking the views of clinical trial participants, researchers, developers, manufacturers, sponsors, investigators, healthcare professionals, and the wider public to help shape improvements to the legislation for clinical trials.

2. Introduction

Clinical trials

Clinical trials are a critical element of clinical research and are key to advances in medical treatment by demonstrating if medicines are safe and effective in people. Clinical trials may be conducted for a range of purposes, for example to test a new treatment or combination of treatments, or to explore new ways to use existing medicines. Clinical trials may be designed and conducted by commercial, academic, or NHS organizations and funded from commercial, government or charitable sources. Examples include trials developed by a pharmaceutical company to support a new product being marketed in the UK or those carried out by academic institutions to generate information about the most appropriate ways to use existing treatments. It is of the upmost importance that all trials are carried out to the appropriate standards, ensuring the safety of participants taking part in the trials, and to ensure that the results generated are reliable, such that decisions can be made about the treatment or intervention being studied.

Regulation of clinical trials

The UK legislation that governs clinical trials sets out the requirements that those conducting a clinical trial, the trial 'sponsors', need to comply with. In the UK these are regulated and overseen by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA) with the UK Research Ethics Service.

In line with international standards, before a clinical trial of a medicine can begin, a Research Ethics Committee (REC) must give a favourable opinion and the MHRA must issue an authorisation. A clinical trial sponsor must make an application, which includes the trial protocol, explaining how the clinical trial will be conducted (e.g. setting out the objectives, design, methodology, and organisation), and how safety of trial participants and reliability of results will be ensured. RECs review research proposals and give an opinion about whether the research is ethical, including looking at issues such as the participant involvement in the research. The MHRA assess the safety and scientific value of the clinical trial, and the pharmaceutical quality of the medicinal product, ensuring that the safety monitoring, reporting and participant follow-up measures are appropriate for the trial. The MHRA will also inspect organisations that conduct clinical trials to verify that they are conducted in line with the appropriate standards (referred to as Good Clinical Practice).

With innovation in treatments and technologies, the way in which clinical trials are set up and operated is evolving. Trials for different purposes are run in different ways, and we need to move away from a 'one size fits all' regulatory approach to

enable flexibility and proportionality. Our regulation needs to support ongoing innovation in the design and delivery of trials, whilst continuing to ensure the safety of all trial participants. This will support more innovative, high-quality and efficient clinical trials across the UK.

Policy objectives

The aim is to update and strengthen the current clinical trial legislation to:

- Promote public health and ensure protection of participants remains at the heart of legislation
- Remove obstacles to innovation, whilst maintaining robust oversight of the safety of trials
- Streamline the regulation of clinical trials and reduce unnecessary burden to those running trials by embedding risk proportionality into the framework
- Facilitate the evaluation and development of new or better medicines to reduce the burden of disease on patients and society
- Ensure the legislation builds international interoperability so that the UK remains a preferred site to conduct multi-national trials.

Details of the proposed legislative changes are set out in the below sections. These intend to improve the speed and efficiency of approvals, support innovation, enhance transparency, encourage greater risk proportionality, and promote patient and public involvement in clinical trials. There are some blockers to innovation and overly prescriptive requirements in the current legislation that we have aimed to identify and remove where appropriate, whilst still ensuring regulatory oversight of trials. We are also aiming to update trial terminologies to reduce any confusion or duplication of requirements for multi-country trials.

We wish to make legislative changes to support streamlined, efficient, and innovative research. We do not wish to extend the scope of the current legislation or add legislation where it is more appropriate and flexible to develop best practice guidance or promote pragmatic interpretation of existing legislation. To further support this we are also considering how best to ensure that, unless required on an emergency basis, guidance will be co-developed with relevant external experts and stakeholders, including patients and trial participants and how we can work with stakeholders to ensure consistent and pragmatic interpretation of legislation.

The proposals outlined in this consultation are intended to streamline and simplify the legislation whilst ensuring trials will be centred on participants, to deliver a regulatory regime that is in the best interests of the research sector and trial participants. The Medicines and Medical Devices Act ensures we can remain responsive to the evolving needs of UK research and provides the powers to enable future changes to be made to the clinical trials regulations as necessary to further improve the clinical trials landscape.

These proposals have been developed by the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority (HRA), in collaboration with an Expert Working Group of stakeholders from across the clinical research sector, including patient representation.

3. Proposals

3.1 Patient and public involvement

Involving people with relevant lived experience in the design and development of research can improve its quality and relevance to participants. Currently, Research Ethics Committees expect researchers to involve patients and the public in the design, management, conduct and dissemination of research. However, the clinical trials legislation is silent on patient and public involvement. Making this a requirement in legislation would send a strong message that trials must be centred on the participants as standard practice to achieve the best outcomes. This should also ensure that trials are as inclusive as possible; involving patients in the design of trials will address barriers to participation and ensure consideration of any issues from the patient perspective. Early feedback from those running trials is that a legislative requirement could support this activity. There is also strong support from research organisations, patients, and their carers.

- The proposal is to ensure protection of participants remains at the heart of legislation, together with introducing a requirement to work in partnership with people and communities (including patients and carers who have experience of living with the relevant condition) in the design, management, conduct and dissemination of a trial, or explain to the ethics committee as part of the application, why this is not appropriate.

To avoid a one size fits all approach and to make the involvement meaningful, the legislation would be supported by clear guidance for applicants, unified messaging across funders and regulators, and consistent review by ethics committees. The provision to support involvement in study design, management, conduct and dissemination should be seen as part of a wider effort to embed patient engagement in the full development pathway for medicines.

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/No

Please provide any further detail to your answer, including how you think this could be best implemented

3.2 Research transparency

Transparency about what clinical trials are being carried out and their findings, benefits the research community, participants, the public, health professionals, commissioners, policy makers, and funders. We want to ensure trusted information about clinical trials is publicly available for the benefit of all. Currently, the clinical trials legislation is silent on transparency, however good practice guidance is in place. We propose to legislate for some of the research transparency provisions policies and processes set out in the HRA 'Make it Public' strategy to embed research transparency in the regulation of clinical trials.

- In line with international standards, introduce a requirement to register a trial in a World Health Organization compliant public register prior to its start and to publish summary of results within 12 months of the end of the trial, unless a deferral is agreed by or on behalf of the Research Ethics Committee.
- To ensure protection of participants remains at the heart of legislation, introduce a requirement to share clinical trial findings with participants in a suitable format within 12 months of the end of the trial, or explain why this is not appropriate.

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

Yes/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

3.3 Clinical trial approval processes

There are a number of changes we could make to update the processes for clinical trial approvals set out in Part 3 of the current UK legislation. These changes would be to reflect that we have left the EU, to support more proportionate regulatory requirements, and to simplify and streamline processes. Streamlining processes will support quicker timelines for overall trial approval compared with the current processes, and provide a competitive advantage, encouraging sponsors to run trials in the UK.

Combined regulatory and research ethics approval

Currently, legislation dictates that the application for a trial regulatory approval is separate to an ethics opinion. A trial sponsor (or nominee) applies to the MHRA for regulatory approvals, whilst the chief investigator of the trial separately applies for a Research Ethics Committee (REC) opinion. The MHRA and HRA, with the UK Research Ethics Service, have been piloting the combined review service over the last 18 months, which offers a single application route and co-ordinated regulatory and ethics review leading to a single UK decision for a clinical trial. We would like to embed this process into the legislation.

The proposal is to:

- Amend the legislation to enable sponsors to make a combined MHRA / research ethics application submitted through a single UK 'front door', the Integrated Research Application System (IRAS). However, the intention is to avoid blocking the ability to make separate applications as an exception.
- To support a combined ethics and regulatory submission, we would also introduce a streamlined appeal process to enable a single process for a sponsor to appeal the joint decision. The legislation would allow for an appeal but the detailed process for appeal would be set out in guidance.
- We propose that the legislation sets out new maximum standard timeframes for the joint review and decision on a clinical trial application. A maximum timeframe would be 30 days from acknowledgement of a valid application for the combined regulatory and ethics committee review of an application, after which an approval would be issued, or if necessary, a request for further information. The UK currently offers expedited timeframes for phase 1 healthy volunteer trials and our intention is to continue to support these early phase studies in the combined system. For multi-national/global trials we would aim to minimise, and ideally avoid, UK-specific changes in how a trial is conducted caused by non-concurrent assessment procedures from multiple regulators in different countries. To support this, we propose to provide for a generous time period (nominally 60 days but with flexible extension) for a sponsor to respond to any requests for information raised which would facilitate the harmonisation of international protocols and better align requests for changes from multiple

regulators. This should assist with sponsors' preparation of requests for further information and avoid application rejections. On receipt of the information requested the final decision would be made within a maximum of 10 days. This means the overall timeframe is internationally competitive, service-orientated and driven by the sponsor (e.g. if the sponsor responded to a request for information within one day the maximum timeframe would be 41 calendar days rather than the current calendar 60 days).

- Where independent advice from the Commission on Human Medicines and/or its Expert Advisory Group(s) may be required, we would continue to allow for extended timeframes. This would apply to certain higher risk products/trials, in line with current UK legislation for clinical trials, for example for certain advanced therapy medicinal products (but not limited to these products). It is proposed that an additional 60 days is added to the initial assessment timeframe to obtain independent expert advice, when required (with the same time added if the review of the response to requests for further information also requires independent expert advice). MHRA has published guidance on the types of trials that may be subject to the regulator seeking advice.

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?

Yes/No

Please provide any further detail to your answer

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

Yes/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

- The current legislation does not explicitly allow a sponsor to withdraw their trial application to the MHRA once assessment of the application has started. This may result in a rejection of the application, causing issues for funding and timing of the trial. We propose to allow withdrawal of the combined MHRA/REC application by the sponsor up until the final assessment decision is issued, with a proportionate fee paid.

- The current legislation allows for a clinical trial approval to remain valid indefinitely, even though wider changes e.g. in medical practice, could impact whether a decision to approve a trial is still appropriate in the future.
  We propose to introduce a sunset provision on approvals, such that the approval will lapse if no participant is included within a specified period of time (for example within 2 years of the trial approval). The intention is that if no participants are enrolled after the specified time period, the clinical trial approval will lapse, or the sponsor will need to apply for an extension. The timeframe would need to provide sufficient flexibility for the sponsor (for example trials in rare diseases can have more difficulty recruiting patients due to the small population size), whilst ensuring that changes in medical practice do not have a significant impact on the benefit/risk of the trial. The timeframe could be specified in the legislation, or in accompanying guidance.

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/No

If yes, do you consider this would be best introduced by:

2. Legislative change with the time limit specified in the legislation
3. Legislative change with the time limit specified in guidance
4. Legislative change allowing for exemptions if a good rationale is provided in the protocol and approved by the competent authorities

- Schedule 3 of the current legislation provides requirements on the “particulars and documents that must accompany an application for an ethics committee opinion, a request for authorisation, a notice of amendment and a notification of the conclusion of a trial”. In order to remain agile and responsive to future changes and innovation in research, we consider this information should be in the form of guidance, and therefore propose to delete schedule 3.

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

Yes/No

Please provide any further detail to your answer

Requests for information (RFIs) and amendments

Following review, if a trial application does not have sufficient information, or where changes to the submitted information are required, the MHRA and/or Research Ethics Committee will issue a Request for Further Information (RFI). The RFI step reduces the chances of an application being rejected, because any missing information or changes necessary to support the application is requested. However, RFIs may delay the application process, because assessment of the application will not continue until a full response is received from the sponsor. Currently RFIs are sent as one communication to the trial sponsor and require a single response from the sponsor.

Learning from clinical trials during COVID-19 has highlighted the opportunity for greater flexibility in the formal communication between applicants and regulators during the review of a clinical trial application. We are proposing the following:

- To support sponsors and their teams, and build a more efficient way for sponsors to answer questions, we propose to allow for a RFI on a particular part of the trial (e.g. a joint MHRA/REC clinical RFI, non-clinical, pharmaceutical) to be issued when it is ready within a maximum timeframe (30 days from the acknowledgement of receipt of the application). This approach worked well during COVID-19 on an informal basis and ensuring there are no blockers to this in legislation would facilitate this option for a broader range of trials when appropriate. The intent for legislative amendments in relation to RFIs would be to remove blockages and enable more flexibility in when an RFI can be given, rather than introduce a complicated process in legislation.
- After approval of a clinical trial has been given, if the sponsor wants to change any aspect of a trial that may have a substantial impact on the safety of trial participants or on the reliability and robustness of the data generated, then a substantial amendment is required and the amendments must be submitted

for approval. Currently, amendments can only be approved or rejected. We propose to allow the possibility of a RFI step for substantial amendments, as this will reduce chances of these being rejected.

- We intend to continue to allow parallel amendment submissions in the UK for different documents therefore speeding up UK processing times and avoiding unnecessary pauses to trial conduct while waiting for approval for changes on a one-by-one basis.
- We also propose to clarify when a substantial amendment is required if a trial is being temporarily halted by the sponsor. We want to ensure that an approval via a substantial amendment is only required in the event a trial is halted, or resumed after being halted, for safety reasons. However, if a trial is stopped for non-safety related reasons e.g. logistical reasons, then a substantial amendment would not be required. This will further support greater proportionality in our regulatory requirements.

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/No

Please provide any further detail to your answer

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

Yes/No

Please provide any further detail to your answer

Notification scheme for low-intervention trials

The proposed notification scheme is a way through which a sponsor can notify the MHRA about a clinical trial where the risk is similar to that of standard medical care, and the clinical trial can be approved without the need for a regulatory review. It should be noted that ethics review will still be required. A notification scheme currently exists in MHRA guidance. However, there has not been high uptake to this scheme. We would like to introduce the concept of a notification scheme into the

legislation which we believe will embed more risk-proportionate approaches into trial conduct.

Below we have outlined further detail about a notification scheme, how a low-intervention trial could be defined, and the kinds of trials that could be eligible for a notification scheme. We would aim for the legislation to include the concept of the notification scheme. To ensure suitable flexibility, we intend for guidance to set out the detail of the scheme and which trials would be eligible.

Definition of a low-intervention trial:

Following the Organisation for Economic Co-operation and Development, the European Union, and MHRA definitions for risk stratification, a low-intervention trial may be described as follows:

Trials where the risk is similar to that of standard medical care, e.g. they involve marketed product(s) either used in accordance with the marketing authorisation or supported by (nationally accepted) published evidence and/or guidance and /or established medical practice.

Advantages of a notification scheme for trial sponsors:

- Low-intervention trials can be conducted in a risk-proportionate manner, and if chosen for inspection will be inspected as such
- No grounds for non-acceptance will be raised by MHRA (since there would be no regulatory review), potentially resulting in a much faster approval
- No substantial amendments to the MHRA would be required as long as the study remains eligible for the notification scheme. However, substantial amendments to the research ethics committee would continue to be required.
- Sponsors would be able to refer to the most up to date Summary of Product Characteristics for the Reference Safety Information (no substantial amendment needed for updates)
- Development Safety Update Reports would not be required (the annual progress report would be sufficient with no line listings)

Submission requirements for a notification scheme:

The submission requirements are the same as for any trial using marketed products via Integrated Research Application System. On submission, the trial sponsor will declare that their trial is low-intervention and complies with the entry criteria for the notification scheme. Once the research ethics committee has issued a favourable opinion the combined decision will be a UK approval. Substantial amendments do not need to be submitted to the MHRA for notification scheme trials, as long as the modification to the trial does not change the status as a low-intervention trial or the eligibility for the notification scheme.

Notification scheme trials are not excluded from Good Clinical Practice inspections but are less likely to be selected in routine inspections on the basis of the risk-proportional approach to selection of individual trials and organisations for inspection.

Some examples of low-intervention clinical trials would be trials involving medicinal products authorised in a country on the approved country list if:

- they relate to the licensed range of indications, dosage and form or
- they involve off-label use (such as in paediatrics and in oncology, etc) if this off-label use is established national practice and supported by sufficient published evidence and/or guidelines or
- they involve a new indication where there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population or
- they involve reducing the exposure to the medicinal product if this does not expose the trial participant to lack of efficacy, or
- they involve targeting the medicinal product to a subtype or subpopulation of the licensed indication or
- they involve the licensed indication, dose, and form but in a different schedule (such as earlier in the treatment pathway)

To be eligible for a notification it is proposed that:

- the trial meets the definition of low-intervention
- the IMP is licensed in UK
- if the trial design includes prospective adaptations, all future adaptations need to be consistent with the definition of a low-intervention trial
- Any placebo used in the trial is either a marketed product (e.g. saline) or has been manufactured under an MIA(IMP) with a formulation that matches the marketed product, with the exception of removal of the active substance. The use of placebo must not expose trials participants to a risk that diminishes their standard of care.
- the primary purpose of the trial is not licensing intent

Where a trial that is eligible for notification has been submitted for ‘standard’ regulatory review, the regulator should liaise with the study sponsor to agree if the submission should continue via the notification route and reclassify as appropriate.

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

Yes/No

If no, please explain any concerns you may have with such a scheme being in legislation

If yes, do you agree that the subset of trials outlined would be appropriate to be eligible for a notification scheme?

Yes/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

3.4 Research Ethics Review

Research ethics review safeguards the rights, safety, dignity and well-being of people taking part in clinical trials. The review is carried out by Research Ethics Committees (RECs), which are co-ordinated by the Health Research Authority and the Devolved Administrations.

The current legislation, in part 2 and Schedule 2, sets out the requirements for a Research Ethics Committee. We propose to streamline requirements for the make-up of an ethics committee and delete the current granular requirements by:

- Updating the requirements for the make-up and minimum number of members including updating the definitions of lay and expert members in line with international requirements, retaining the requirement for a mix of lay and expert members.
- Delete schedule 2 of the current legislation, which includes very restrictive and granular provisions on the make-up, proceedings, support staff, premises and facilities relating to ethics committees, and instead refer to guidance/HRA policy which will allow for greater agility in decision making.

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

We wish to promote and encourage the inclusion of underserved populations such as pregnant and/or breast-feeding individuals, and increase diversity in clinical research, whilst ensuring participant protection throughout the trial. Best practice guidance can go some way towards encouraging wider representation in the recruitment of trial participants; however, we could introduce into legislation requirements to support this.

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

Yes/No

Please provide any further detail to your answer

If yes, what legislative requirements could be introduced to better support increased diversity in trial populations?

3.5 Informed consent in cluster trials

In many cases we do not always know (due to a lack of evidence) which medicine is best for an individual patient, or group of patients. The best way to reliably compare the different treatments available and get the evidence needed to inform treatment decisions is by conducting large-scale randomised controlled trials.

One way of doing this is by conducting so called “cluster” trials. Cluster trials are conducted on existing approved medicines, where randomisation to a certain treatment is pre-determined by location, for example all participants in one hospital would receive Drug A and all participants in another hospital would receive Drug B.

Such trials present little or no additional risk to the participant as they would be randomised to receive a standard treatment routinely prescribed for their condition. The patient would not need to do anything other than take the treatment as normal and the data needed for the trial would be extracted from their medical notes.

Under the current legislation, ‘cluster’ trials can only be undertaken if every participant actively provides their written consent after being given detailed information about the trial in an interview with one of the investigators. Simplifying the way that informed consent can be obtained for cluster trials will support and promote their use and facilitate the gathering of real-world data to inform best practice in a way that is more proportionate to the low level of risk involved. This approach should encourage wider uptake into lower risk trials. The introduction of this simplified means of seeking agreement from participants will make these types of low intervention trials more feasible and therefore widen the reach and participation of this type of research.

We propose to:

- Streamline requirements by introducing a simplified/low burden means of seeking agreement from participants for low-intervention clinical trials where the investigational medicinal product is pre-determined based on location and are used in accordance with the terms of the marketing authorisation (e.g. “cluster trials”)

More generally, legislation should enable flexibility on consent provisions, ensuring consent is sought to the correct standards, but more proportionate approaches to seeking consent where the risk is lower are available.

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

Yes/No

Please provide any further detail to your answer

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?

Yes/No

Please provide any further detail to your answer

3.6 Safety reporting

When a clinical trial is running there are a number of requirements for sponsors to report potential or emerging safety risks to the MHRA or make these known to investigators in the trial. We are committed to ensuring the highest standards of participant safety while taking the opportunity to remove reporting requirements that add burden to investigators but do not contribute to participant safety. We have identified a number of changes where this may be possible:

- A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction that has not been previously associated with the medicine but is suspected to be caused by the medicine under investigation in the clinical trial. These reactions are currently required to be reported to MHRA in an expedited timeframe. We propose to remove the requirement for individual SUSARs to also be reported to all investigators. This will reduce the burden on sponsors and investigators without impacting on participant safety. Informing Investigators of safety information is better met via the Investigator's Brochure (a comprehensive summary of clinical and non-clinical data about the medicinal product compiled throughout the study), which is updated at least annually. A list of SUSARs without background information and proposal of appropriate risk mitigation actions is generally not very helpful.
- We also propose removing the requirement to report SUSARs and annual safety reports to RECs. We foresee the MHRA will lead on assessment of these and liaise with RECs as necessary. These proposals are to remove duplicative reporting requirements and would not reduce oversight of participant safety.
- Currently each SUSAR needs to be reported to the MHRA in an expedited manner. We would like to introduce further flexibility in the reporting of SUSARs. We propose that, where justified and approved by the regulatory authority, SUSARs can be reported in an aggregate manner, provided that the trial protocol mandates continuous monitoring of serious adverse events/reactions. If aggregate reporting is approved, the Sponsor should be assisted in reviewing safety data by a (independent) Data Monitoring Committee.

- In order to support flexibility in reporting SUSARs as above, we propose to introduce a legal requirement for the sponsor to have a safety monitoring (pharmacovigilance) system aimed at periodically reviewing accumulating safety data in order to detect safety signals and propose appropriate risk mitigating actions. The pharmacovigilance system should be risk proportionate and will be specific for a medicinal product if the trial Sponsor is the manufacturer or marketing authorisation holder. The pharmacovigilance monitoring will be trial-specific for non-commercial Sponsors.
- Remove the requirement to include listings of serious adverse events and serious adverse reactions in annual safety reports (Development Safety Update Reports). The reports should instead include an appropriate discussion of signals/risks associated with the use of the medicinal product as well as proposed mitigation actions.
- When an investigator or Sponsor takes an appropriate Urgent Safety Measure during a trial to protect participants from an immediate safety risk, they are expected to notify the regulator as soon as possible (this is usually via a phone call within 24 hours of the measure being taken) and also provide written notice to the MHRA, currently within 3 days. We propose to extend this written notification from no later than 3 days from when the measure was taken, to no later than 7 days to promote international harmonisation of reporting windows.

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.

Yes/No

Please provide any further detail to your answer

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.

Yes/No

Please provide any further detail to your answer

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

Yes/No
Please provide any further detail to your answer

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?

Yes/No

Please provide any further detail to your answer

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?

Yes/No

Please provide any further detail to your answer

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

Yes/No

Please provide any further detail to your answer

3.7 Good Clinical Practice

Good Clinical Practice (GCP) is a set of internationally recognised ethical and scientific quality requirements for designing, conducting, recording, and reporting clinical trials that involve people. The current UK legislation on clinical trials (in schedule 1 part 2) sets out that the principles of GCP must be followed to conduct a clinical trial, and MHRA conduct GCP inspections to ensure Sponsors conduct trials according to GCP and the trial protocol. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP is usually followed where trials are conducted to support a marketing authorisation, although this is not a UK legislative requirement.

We are proposing to maintain a requirement for compliance with broad principles of GCP to protect the rights and well-being of trial participants and the reliability of the trial results. We are not proposing to adopt a specific set of GCP requirements or move to legislate for ICH GCP in its entirety but maintain a requirement for compliance with principles of GCP. UK principles would be written into legislation but sponsors will still be able to choose to follow ICH GCP when producing data for marketing authorisation purposes. We propose to update the current GCP principles to ensure that they are flexible and can be applied to a broad range of clinical trials. They will include identification of critical to quality factors, risk proportionality, and will support more efficient approaches to trial design and conduct

We propose to allow for an overarching risk assessment and adaption approach across the whole of the UK Clinical Trials framework, so that proportionality is not limited to specific areas, but instead the trial is risk assessed in its entirety and managed appropriately based on that risk assessment.

We are proposing a number of specific changes in relation to GCP:

- As part of the drive towards risk proportionality, we propose to clarify in legislation that regulators should take a proportionate approach throughout the clinical trial life cycle. For example, to adopt similar wording to the Care Act 2014, which requires the HRA to seek to ensure that such regulation is proportionate. We recognise that embedding risk-adapted trial conduct in practice needs to be encouraged by all parties i.e. regulators and those conducting trials.
- We are seeing a huge increase in the use of electronic systems in all aspects of trial conduct, not just Case Report Forms (CRFs) but Interactive Response Technology (IRT) systems, Patient Reported Outcomes, Consent, web portals for documentation sharing and training etc. These systems can have a direct impact on patient safety, data integrity and protocol compliance. Currently these systems may be designed or controlled by service providers external to the trial, and GCP may not be applied. For example, we have seen an IRT system fault that resulted in overdose for patients who had previous safety related dose

reductions. We would like to future proof the applicability of GCP for electronic systems by introducing into legislation clarity over the design and control of electronic systems that impact on safety and results. This would include a responsibility for service providers, as well as Sponsors, to follow the principles of GCP.

- Sponsors are required to keep a repository of information, such as documents and data, known as the Trial Master File. This is to allow for appropriate reconstruction of the trial and to demonstrate that it has been conducted in accordance with GCP requirements and the clinical trials regulations. This is particularly important for trials that are intended to support a marketing authorisation as it is part of ICH GCP. The documents to be filed in the Trial Master File should be essential documents, created during the conduct of the study, to demonstrate what was done. As a result, the content of the TMF should be proportionate to the trial conduct. The checklist in ICH GCP has led to the creation of documents specifically for filing purposes, and the advent of electronic Trial Master Files has introduced a complex and cumbersome filing system. We want to ensure that Trial Master Files are proportionate and reduce the focus on extensive filing. It is proposed to amend the legislation, so that there is a requirement for a proportionate Trial Master File, that must be directly accessible to MHRA inspectors, that it is retained for a minimum of 25 years, but that more detailed aspects, such as proportionality in the retention period, are covered in guidance.
- As a participant in a clinical trial, patients and volunteers do not have to pay for the investigational medicine they receive as part of the trial. We would like to make it clear that participants should also not be liable for treatment costs such as scans and consultations where a trial is being run by a private clinic, to make it clear that the participant should not bear a financial cost to take part in a clinical trial.

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?

Yes/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

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

Yes/No

Please provide any further detail to your answer

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

3.8 Sanctions and corrective measures

To ensure that our regulatory oversight to protect public health is both proportionate and strong, we are considering more risk proportionate corrective measures and introducing an additional proportionate sanction to those that are already in existence such as financial penalties and infringement notices (details of which are set out in Part 8 (Enforcement and Related Provisions)) of the current UK clinical trials legislation.

- Currently, regulators may have information or evidence of serious non-compliance of a Sponsor or an investigator, but if that Sponsor were to submit another Clinical Trial Application, then we are not able to take knowledge of their current serious non-compliance into consideration when assessing the new application and therefore we may potentially be putting participants at unnecessary risk. We therefore propose to introduce the ability for regulators to refuse to approve a new study based on ongoing serious non-compliance with the legislation, where there could be significant harm to participants. The ability to do so will ensure the safety of participants in new trials. We anticipate that this will be a power rarely used, but as a Regulator it is imperative that we are able to take action when absolutely necessary to safeguard patients. For example, we consider this would only be used in instances where the non-compliance was so serious that it would result in regulatory action, such as an Infringement Notice, termination of a trial or possible prosecution. We would also propose to introduce in the legislation the right to appeal the grounds for non-acceptance (GNA), via a process that would include an independent review of the GNA.

- We would like to improve the clarity on the suspension or termination of a clinical trial (Regulation 31 of the current legislation) to reflect modern trial design. The legislation currently indicates that regulatory action means that the whole trial would need to be stopped. Instead, we want to make clear that regulatory action might apply only to a specific part of the trial e.g. recruitment, dosing, a specific arm of the trial or related to a particular trial site. This change would help ensure that regulatory actions are proportionate and recognises the increasing use of innovative trial designs.

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/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

3.9 Manufacturing and assembly

The current clinical trial regulations set out requirements for the manufacture and import of investigational medicinal products to be used in clinical trials, as well as how these products should be labelled (Part 6 & Schedules 6-8). It is not our intention to align with the upcoming European Clinical Trials Regulation Annex 6 labelling requirements (the Clinical Trials Regulation (Regulation (EU) No 536/2014), which comes into application on 31 January 2022). We propose to update the following:

- New European Union legislation introduces concept of auxiliary medicinal product. These are medicinal products used in a trial but which are not the investigational product, a similar concept of “non-investigational medicinal products” are currently managed through guidance. We propose to introduce into legislation the term “non-investigational medicinal product”, which would allow us to extend the concept to non-medicinal products that may currently be unregulated (such as non-medicinal ‘challenge agents’).

- We propose to introduce risk-proportionate requirements in UK legislation for the labelling of investigational medicinal products such as those with a marketing authorisation and medicines manufactured at the point of care. We would like to allow the sponsor to propose risk adapted labelling. This provision would allow for such products to have reduced or no clinical trial specific labelling if justified.

- Currently the only UK exemption (in regulation 37) to holding an authorisation for certain IMP activities conducted in a hospital or health centre is for assembly (packaging / labelling). We would now like to make an exemption from the need to hold a Manufacturers Authorisation for IMPs (MIA(IMP)) for the preparation of radiopharmaceuticals used as diagnostic IMPs where the process is carried out in hospitals, health centres and clinics. Whilst exempt from requiring an MIA(IMP), radiopharmaceuticals used in a clinical trial would still need to be manufactured to an appropriate level of GMP, e.g. at a site holding a manufacturing specials licence.

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/No

Please provide any further detail to your answer

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/No

Please provide any further detail to your answer

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?

Yes/No

Please provide any further detail to your answer

3.10 Definitions and other terminologies

We propose to update a number of definitions in the legislation to update UK terminology and promote international harmonisation of definitions. This will also introduce into legislation risk-proportionate definitions, which are already set out in UK guidance. For example, changes to definitions we are considering are outlined below. We expect that drafting of the legislation to reflect the proposals outlined in the sections above may also require in changes and updates to related definitions.

- Update to definitions of ‘clinical trial’, ‘clinical study’, ‘low intervention trial’, and ‘non-interventional trial’ to promote international harmonisation. It is, however, proposed to maintain the UK definition of a ‘substantial amendment’ as stakeholders consider that this provides good clarity.
- Replace the term ‘subject’ in current legislation with ‘participant’. The term ‘subject’, used to describe someone taking part in a clinical trial, is now viewed as outdated and the legislation should reflect more appropriate terminology.
- Since we have now left the EU, we will no longer require a EudraCT number (the unique trial number provided to each trial through the EU database). Instead, we will require a UK specific reference (the IRAS number) and therefore should remove the requirement for a EudraCT number from legislation. The IRAS number will be automatically assigned during preparation of an application and will not represent a burden on the applicant.

- Simplify the current legislation (Regulation 3) to clarify the role of sponsors and the ability to co-sponsor trials. Role and responsibilities in co-sponsored trials would be set out in UK guidance.
- To reflect the range of roles in research teams, we will clarify that informed consent may be sought by any member of the investigator's team, qualified by education, training or experience, appropriate to the trial, in line with the current version of the Declaration of Helsinki.
- Facilitate trial conduct by expanding the professional groups who can be an Investigator (e.g. expand to air ambulance paramedic) as currently defined in the definitions for 'authorised health professional' and 'health care professional' and clarify in guidance how the chief investigator and other coordinating investigators, and sponsor and co-sponsors can work together in platform trials.
- Remove a burden by allowing data collection after MHRA early access approval without need for Clinical Trial Authorisation (which would facilitate 'real world' data collection) i.e. to clarify that where the MHRA has approved access to an unlicensed medicine (such as via the Early Access to Medicines Scheme), 'non-interventional' real world data collection as part of that approval may be considered as an 'authorised' indication and not an interventional Clinical Trial of an Investigational Medicinal Product. Research Ethics Committee review may still be required as necessary, as such trials would still be regarded as clinical research.
- Clinical trials may require follow-up of participants years after the intervention being studied has stopped, for example to look at survival rates in cancer trials or advanced therapy trials. We propose to remove obstacle to this by allowing 'non-interventional' long term follow up information to be collected after intervention end without the need for regulatory approval.

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

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

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/No

Please provide any further detail to your answer

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?

Yes/No

Please provide any further detail to your answer

3.11 Conclusion

We consider that the proposals outlined balance introducing improvements to remove burdens and obstacles to sponsors carrying out clinical trials whilst ensuring the focus remains on protection of those participating in trials. We are proposing to remove the aspects of the legislation that are more prescriptive, in favour of introducing greater flexibility and more risk-proportionality, to reflect that trial design and operation is evolving with innovations in the products that trials investigate. New requirements proposed are intended to ensure that trial participants and their safety are at the heart of the legislation.

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

Yes/No

Please provide any further detail to your answer

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?

40. Are there potential costs or financial implications of the proposals outlined that you think we need to especially consider? Please provide any evidence or comment that would help us develop the cost/benefit analysis on the proposed changes.

In Northern Ireland new policies must be screened under Section 75 of the Northern Ireland Act 1998, which places a statutory duty on public authorities, to mainstream equality in all its functions – so that equality of opportunity and good

relations are central to policy making and service delivery. In addition new or revised policies must be rural proofed in line with the Rural Needs Act (NI) 2016 which requires public authorities to have due regard to rural needs.

41. We do not consider that our proposals risk impacting people differently with reference to their protected characteristics or where they live in NI.

Do you agree?

Yes/No

We welcome any further views on this point.

42. Do you think the proposals could impact people differently with reference to their [or could impact either positively or adversely on any of the] protected characteristics covered by the Public Sector Equality Duty set out in section 149 of the Equality Act 2010 or by section 75 of the Northern Ireland Act 1998?

Yes/No

Please provide any further detail to your answer

43. Do you have any evidence that we should consider in the development of an equality assessment?