Medicines & Healthcare products Regulatory Agency

Government response

Consultation on legislative proposals for clinical trials

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Foreword

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Clinical trials are our means of safely bringing pioneering new treatments directly to patients and are a key step to healthcare innovation. They enable us to find new ways to treat conditions that affect people up and down the country every year. The UK's regulatory environment for clinical trials is already strong, with the Medicines and Healthcare products Regulatory Agency (MHRA) recognised as a global leader. The regulatory response to COVID-19, for example, demonstrated the rapid, robust and agile capabilities of the UK system. Our departure from the European Union provides an unparalleled opportunity to build on this foundation to advance how clinical trials are regulated across the UK.

It is also clear that the UK's position in the global clinical trial landscape has shifted, as other countries recover their delivery performance post-pandemic, providing attractive alternatives in what is a highly competitive field. We must therefore capitalise on the opportunity in front of us to strengthen and improve the regulatory environment, whilst minimising regulatory burdens on clinical trial sponsors.

It is welcome that the MHRA, working closely with the Health Research Authority, has been thinking and engaging with stakeholders on the regulation of clinical trials. The changes set out in this response will serve as a basis for and align with other initiatives, including the work of Recovery, Resilience and Growth partners, the review of clinical trials led by Lord O'Shaughnessy and work being undertaken with Sir Patrick Vallance on the life sciences regulatory environment. Collectively, the UK regulator, system partners and the clinical research sector will work together to maximise the potential to accelerate innovations that are of particular significance to patients and the NHS.

Our approach to regulation will continue to prioritise the safety and efficacy of healthcare interventions. The reforms taken forward here will strengthen this approach whilst delivering a stable and streamlined framework following the UK's departure from the European Union. They will also establish a robust, progressive baseline from which the UK can develop innovative regulatory approaches to rapidly emerging science and technologies.

These reforms are just the beginning of the UK's journey to becoming a transformational, global regulatory leader, as outlined in the Life Sciences Vision. There will be further opportunities to evolve the UK's regulation, make step changes in our approach to patient safety and enhance the UK's global competitiveness, for example through the use of real-world evidence, novel analytics and data tools, allowing closer integration with the work of other system partners such as National Institute for Health and Care Excellence.

Working in partnership with likeminded regulators globally will also be key, building on collaborations such as the FDA's Project Orbis and the Access Consortium (Australia, Canada, Singapore and Switzerland). The UK can play an enthusiastic role advancing innovative approaches with its global peers through deepening cooperation, such as with the

FDA, as well as in global standard setting forums such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals of Human Use.

Clinical trials are evolving to find innovative ways to bring new treatments to patients faster and more effectively. The views shared through this consultation from patients, industry, academia and the healthcare sector, have informed a set of reforms that will deliver a more agile and flexible UK regulatory framework to support that continued innovation.

Executive Summary

The MHRA and the Department of Health in Northern Ireland consulted on a set of proposals to update, improve and strengthen the UK legislation that underpins the regulation of clinical trials. Having analysed over 2000 responses, we will now take forward legislation to reform the UK clinical trials regulatory framework that will:

- **Ensure patients and their safety are at the focus of all clinical trials and bring the benefits of clinical trials to everyone**

  We are committed to ensuring new medicines are safe and effective for the whole population and to reducing health disparities. Clear guidance on diversity in trials will drive a vital shift in representation in, and access to, research, without imposing targets or arbitrary quotas. This will help to ensure that participants come from diverse backgrounds, so the findings of research reflect prevalence and clinical need across the population, and all can benefit from new treatments.

- **Create a proportionate and flexible regulatory environment**

  We will bring forward changes to empower researchers to take more risk appropriate approaches to trials, meaning the regulatory requirements expected will be more flexible to match the risk that a trial presents. For example, we will introduce an overarching duty to consider proportionate approaches, and for trials where the risk is similar to that of standard medical care, a “notification scheme” will enable a clinical trial to be approved without the need for a regulatory review.

- **Cement the UK as a destination for international trials**

  We will introduce more streamlined and efficient application processes, making it easier to apply for trials in the UK but without compromising on safety standards, by legislating for a combined MHRA/research ethics review, with internationally competitive approval timelines and more flexibility for sponsors to respond to questions raised by regulators. We will align with ICH Good Clinical Practice principles for trial conduct, ensuring that UK trials meet international standards, and the UK remains a preferred site to conduct multi-national trials.

- **Provide a framework that is streamlined, agile and responsive to innovation**

  The new framework will ensure legislation is as future-proof as possible and will be responsive to different types of trials and innovative ways of carrying out trials. We will remove granular and duplicative requirements and use guidance to set out specific details. We are committed to working with patients and the research community to co-develop clear, comprehensive accompanying guidance.

This package of changes will deliver on our vision for a more proportionate, streamlined, flexible and effective clinical research environment, putting patients at the heart and the UK at the forefront of innovative regulation for clinical trials.

1. Introduction

The current legislation that governs the regulation of clinical trials in the UK is the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, which is based on the EU Clinical Trials Directive. This legislation sets out the framework for regulating clinical trials of human medicines, covering the authorisation of clinical trials, their ethical approval, the conduct of the trial (including adherence to good clinical practice), the reporting of adverse events and breaches of the authorisation, the manufacture and importation of the medicinal products involved in the trial and their labelling.

Now that we have left the EU, we have the opportunity to reform our national legislation to deliver a world-class sovereign regulatory environment for clinical trials to support the safe development of innovative medicines for the benefit of patients and public health. The MHRA, the HRA and the Northern Ireland Department of Health, put forward proposals to capitalise on this opportunity and consulted on them from 17 January to 14 March 2022.

We proposed to amend the current legislation to:

- Promote public health and ensure protection of participants remains at the heart of legislation
- Facilitate the evaluation and development of new or better medicines to benefit patients and society, and improve public health
- 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 taking a risk-based approach
- Ensure the legislation enables trial sponsors to work across countries so that the UK remains a preferred site to conduct multi-national trials.

The public consultation sought the views of patients, clinical trial participants, researchers, developers, manufacturers, sponsors, investigators, healthcare professionals, and the wider public.

This document sets out our response to that consultation exercise and our next steps.

2. Summary and evaluation of responses

We received thoughtful and considered responses from a total of 2138 respondents, 88% from individuals and 12% from organisations. We thank all those who responded for taking the time to consider the proposals. We were very pleased to have such a high level of engagement from patients and the public, as well as those organisations involved in the design and running of clinical trials.

Individual responders included members of the public, patients, carers, researchers, and health care professionals. Organisational responses came from industry trade associations, academic institutions, individual pharmaceutical companies, not for profit organisations involved in drug development, patient advocacy groups, regulatory/ professional representation bodies and health delivery organisations.

Responses were received from across the UK and internationally, including from European countries, the USA, Australia, Canada, New Zealand, South Africa, Japan and India, and from global organisations.

We have analysed the responses and carefully considered the feedback received. In doing so, we looked at the responses to the questions posed, and the information provided in free text sections. Responders were able to select and respond to specific sections of interest, and therefore some responders did not answer every consultation question.

2.1 Summary of the Government response

We received strong support for the proposals to update and improve the legislation for clinical trials. Most responders agreed that we need to ensure that participant safety remains at the heart of the legislation, and that introducing more flexibility and making decisions based on an assessment of risk will help streamline processes for those running trials. Responses also indicated that collectively the set of proposals will make it easier and more efficient to run trials for new medicines in the UK, and that they will enable greater patient access to new, safe, life-changing treatments and make the UK an even more attractive place to trial new medicines.

Ensuring patient safety was an overarching theme of the responses, and there was strong support for the legislation to **embed public involvement**. Trial participants and their safety have always been our prime consideration and our proposals reflected that this must remain the foundation for all clinical trials. We will ensure greater patient involvement in trials by introducing detailed guidance to support embedding the patient voice into the design and conduct of trials. We will work to ensure participants come from diverse backgrounds, reflecting the clinical needs across the whole population through the development of explicit guidance. We will also ensure increased public transparency about trials that are being carried out and their results.

There was also support for proposals to **streamline processes**, so long as the necessary regulatory oversight to assure safety is not compromised. We will legislate to combine the MHRA and research ethics reviews, and to ensure there is no obstacle to allowing flexibility for sponsors to respond to questions from regulators as they are raised, rather than all at once. There was concern that proposals to streamline safety reporting could reduce participant safety. To assure participant safety, key requirements that ensure both regulators and researchers are aware of potential risks will remain and we will only address the requirements in our current legislation that are duplicative or do not provide additional value in identifying safety risks. We will remove burden in these areas so that investigators can focus their resources on running the best possible clinical trials, to support increased patient access to safe and innovative medicines. This will facilitate good, safe research while ensuring appropriate regulatory scrutiny of trials.

Responses agreed that the legislation should enable more **proportionate and risk appropriate approaches** to trials. We will move away from 'one size fits all' legislation and introduce measures to enshrine proportionality. This will empower researchers to design and conduct the most appropriate trials and enable more modern and innovative trials. We will maintain regulatory oversight but enable flexibility so that requirements match to the kind of trial being conducted. To support this, we will introduce an overarching expectation to consider proportionate approaches. We will provide for a "notification scheme" for low-risk trials to be approved without the need for a regulatory review (but maintaining the requirement for a favourable opinion from a Research Ethics Committee). Finally, we will enable a simplified informed consent process for lower-risk trials which will aid proportionality, ensuring patients will still receive the critical information to consider participation but will be supported to give their consent in an easier way.

Responses highlighted that many sponsors conducting UK trials may also be running the same trial in the European Union and across the world. This reinforces the importance of **international interoperability,** ensuring that trials sponsors can apply to the UK as part of a multi-country trial, and that data generated from UK trials continues to be accepted globally. To support this, we will align with the Good Clinical Practice principles of the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), widely accepted as the international standard to assure safety of trial participants and integrity of trial data. The legislation will balance remaining fully aligned with international standards whilst taking the national measures we outline above to offer agility and flexibility. The feedback received indicates that responders largely agree with us. By improving and streamlining UK regulatory approval and the assessment of trial applications, we can maintain international interoperability to support multi-national trials, whilst making it easier to apply for and conduct trials in the UK. Our legislation will ensure the UK is a preferred global destination to conduct clinical trials and develop innovative medicines.

Following analysis of the consultation, there are four proposals that we are not taking forward:

- Firstly, we proposed enabling regulators to take into account previous information of non-compliance when considering a new clinical trial application. Although this was supported, comments raised important unintended consequences such as a reduction in trials being conducted in the UK and increased reluctance to adopt proportionate

approaches. We expect the measure would be used very rarely, and in light of these concerns, we do not think it would be proportionate to introduce this sanction.

- Second, we sought views on the collection of data on unlicensed medicines. We recently introduced new legislation to support the Early Access to Medicines Scheme, which enables patients to receive a medicine before it receives a license, where there is an unmet clinical need. That legislation made changes to support the gathering of evidence during clinical practice, but outside of formal clinical trials, subject to informed patient consent. These changes deliver on the intent of our proposal, and we do not consider further legislative changes are needed at this time.
- Thirdly, the consultation asked whether we should legislate to ensure the trial population appropriately reflects everyone who could be affected by the condition being studied, through ensuring clinical trial participation reflects the diversity of the UK population, for example ensuring sex balance, participants of different ages and population groups, depending on the condition being addressed. This would give greater ability to assess efficacy and risk specifically in those patient populations. Taking into account the responses received, we consider this is best approached through explicit guidance rather than new legislative requirements, as guidance will allow greater flexibility to update and adapt with new knowledge and experience.
- Lastly, we will be producing guidance on patient and public involvement, which will highlight best practice rather than legislating for this. This will give trials more flexibility, which is important because appropriate patient and public involvement is different at different stages or types of trials. Responses highlighted that legislation could be too prescriptive and add to potential delays to trial set ups, as well as cause an additional administrative burden, which ultimately may be a disincentive for trials to be carried out in the UK. However, we may consider legislating for this in the future.

One further theme raised related to the wider government response to COVID-19, such as marketing authorisation routes and vaccination policy. We only considered comments which related to the regulation of clinical trials or this specific consultation, and so we do not address these points in this document.

The table below summarises each of the proposals put forward in the consultation, and the outcome following analysis of the consultation responses, noting that for many of the proposals we will implement ‘high-level’ legislation with clear supporting guidance, co-created with the community. The following sections summarise and evaluate the responses received to the specific questions asked across each of the different sections of the consultation proposals.

Consultation proposal	**Outcome following consultation analysis**
Requirement for the involvement of people who have relevant experience as a patient, family member or carer, in the design, management, conduct and dissemination of a trial	To be addressed through guidance rather than in legislation.
Requirement to register a trial	Introduce legislative requirement, as outlined in the consultation

Requirement to publish a summary of results within 12 months of the end of the trial unless a deferral has been agreed	Introduce legislative requirement, as outlined in the consultation
Requirement to share trial findings with participants in a suitable format	Introduce legislative requirement, as outlined in the consultation
Combined MHRA and ethics review with initial review of application by 30 days post validation of the application, as standard	Introduce a combined regulatory and ethics approval process into legislation, but keep the option for independent submissions available to allow rare exceptions
Nominal max 60 days to respond to RFI	Introduce legislative requirement, as outlined in the consultation (Legislation to enable longer time period for RFI, if approved by regulator/REC)
MRA/REC have 10 days to provide final decision after RFI response received	Introduce in legislation, as outlined in the consultation
Extended timeframe for assessment of an application, where independent expert advice is required	Introduce in legislation, as outlined in the consultation
Trial approval to lapse if no recruitment occurs within 2 years	Introduce in legislation, but with consideration of exceptions and a clear process for those exemptions
Detail currently outlined in schedule 3 better placed in the form of guidance rather than legislation	Amend legislation as outlined in the consultation
Trial sponsor can have sight of RFI per discipline as they are ready	Ensure the legislation does not restrict ability to do so (rather than introduce a specific provision)
Ability to receive an RFI during the review of a substantial amendment	Introduce in legislation, as outlined in the consultation, with clear timelines
Introduction of a notification scheme for low intervention trials	Introduce in legislation, as outlined in the consultation
Membership or constitution of Research Ethics Committees (including update/deletion to Schedule 2)	Amend in legislation, as outlined in the consultation
Requirements to support diversity	New requirement not taken forward in legislation, to be addressed through guidance.
Flexibility on consent provisions where the trial is considered to have lower risk	Introduce in legislation, as outlined in the consultation
Simplified means of seeking agreement from participants for cluster	Introduce in legislation, as outlined in the consultation

trials using established medicines (existing treatments)	
Remove the requirement for individual SUSARs to be reported to all investigators	Remove from legislation, as outlined in the consultation
Remove the requirement to report SUSARs and annual safety reports to Research Ethics Committees (in addition to MHRA)	Remove from legislation, as outlined in the consultation
SUSARs can be reported in an aggregate manner	Enable in legislation as an option, where justified and approved
Remove the requirement to include listings of serious adverse events and serious adverse reactions in annual safety reports and instead include an appropriate discussion	Enable in legislation as an option, where an appropriate discussion of the risks is provided instead
Extend the written notification for Urgent Safety Measures from no later than 3 days to no later than 7 days	Extend the timeframe in legislation, as outlined in the consultation
Incorporate more elements on risk proportionality	Introduce an overarching expectation for sponsors to identify and document the risks to patient safety and the reliability of the data and conduct the trial in a risk-proportionate manner
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	Clarify in legislation, as outlined in the consultation
Current GCP principles require updating to incorporate risk proportionality and GCP principles to include in legislation	Legislation to reference ICH GCP principles, but not full ICH guidance
Regulators 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	Not taken forward. However, non-compliance with new registration and reporting requirements to be clear as grounds for non-acceptance of a request for authorisation.
Regulatory action to be taken against specific part of a trial where appropriate rather than the trial as a whole	Amend in legislation, as outlined in the consultation
Introduce the term ‘non-investigational medicinal product' into legislation	Introduce in legislation, as outlined in the consultation
Where a medicine is labelled according to its marketing authorisation (and no blinding is	Introduce in legislation, as outlined in the consultation

required) that specific clinical trial labelling may not be required	
Radio pharmaceuticals used as diagnostics in a trial to be able to be exempted from the need to hold a Manufacturers Authorisation for IMPs	Introduce in legislation, as outlined in the consultation, with clarity that another valid type of authorisation will be required
Updates to definitions	Amend legislation, as outlined in the consultation (including facilitating long term follow-up). Do not take forward proposal for retaining current definition of substantial amendment
Data collection following MHRA approval of use of unlicensed medicines	Not taken forward, because addressed in other recent legislation
Expand the professional groups who can be an Investigator	Legislation to enable suitably trained and qualified individuals, and role of Investigator to be clearly defined
Any appropriately trained and qualified member of the investigator's team can seek consent	Amend legislation, as outlined in the consultation

3. Consideration of responses to individual questions

3.1 Patient and Public Involvement

The consultation sought views on introducing legislative requirements for patient and public involvement in the set-up of new clinical trials. Research Ethics Committees currently expect researchers to involve patients and the public in clinical trials, but this is not required by legislation. To ensure participants are at the heart of the legislation we proposed introducing a requirement to work in partnership with people and communities (including those who have relevant experience of what is being investigated in the trial as a patient, family member or carer) 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.

Question 1: Do you agree that a requirement for involvement of people with relevant lived experience in the design, management, conduct and dissemination of a trial, should be included in the legislation?
There were 1407 responses of which:

- 1087 (77.2%) agreed
- 224 (15.9%) disagreed
- 96 (6.8%) had no opinion

There was a strong consensus that patient and public involvement is important in clinical trials. A clear majority of responses agreed to making patient and public involvement in clinical trials a legislative requirement.

Responders considered that involving patients brings valuable insights and important additional perspective that would improve the conduct of trials, and ensure the information provided before, during and after the trial is clear and relevant.

Responders highlighted that clear definitions and guidance which incorporates best practice, would be needed to ensure that meaningful patient and public involvement takes place. There may also be a need for training, particularly for those who are unfamiliar with patient and public involvement best practices.

There was consensus that patient and public involvement should be proportionate to the costs, complexities and risks of a study.

However, responders raised concern about the potential for additional costs, administrative burden, or that legislation would be too prescriptive. Some considered legislation may add to

potential delays to trial set up, particularly if the legislation was not clear enough or act as a disincentive for trials to be conducted in the UK, especially if it goes beyond requirements or expectations in other countries.

Of those who disagreed with the legislative requirement, many considered that existing requirements are sufficient e.g., some trial funders already require public involvement, or felt public involvement to be an ethical issue rather than a legal one and as such, should sit within the remit of research ethics committees (RECs) rather than legislation. Responders also mentioned that it may not be possible to involve patients in all trials. Practical issues were raised, such as appropriate arrangements in rare diseases where small population groups might make involvement difficult. It was also noted involvement may not be needed or appropriate for all stages of a trial, such as in the management of trials. However, the vast majority of those who disagreed with the proposal supported the encouragement of public involvement through other means, such as guidance.

Government response

Responses to this question demonstrated support for involving people who have relevant experience of what is being investigated in the trial as a patient, family member or carer in the development of research. To improve practice and support trials to involve participants further, we will introduce detailed guidance, containing clear definitions. This will keep the new regulatory framework as flexible as possible. We will keep patient and public involvement in clinical trials under review and may consider legislating in the future.

There was clear understanding that public involvement can add enormous value to improve the quality of research and ensure that it is most relevant to those the study is aiming to benefit. However, responses also raised clear concerns that introducing a new legal requirement at this time could ultimately act as a disincentive, leading to trial sponsors choosing not to run their trial in the UK. This would be counter to our goal to increase UK attractiveness and make it easier to run trials in the UK, so that more patients can benefit from innovative clinical research. Detailed guidance will provide the necessary flexibility to make clear our expectations but prevent additional legal burdens on Sponsors.

There is a wide range of ongoing activity across the research landscape to promote patient and public involvement in clinical trials, through guidance, collaborative working between regulators and funders, and practical support for research teams. This work is going a long way to support increased involvement in trials, but would benefit from clearer and more detailed guidance. We will therefore produce detailed guidance enabling further trials to follow suit. In drafting the guidance, our priority will be to ensure that patient and public involvement is meaningful and avoid a one size fits all approach. We will expect the level of patient and public engagement and involvement to be proportionate to the trial itself, and patient and public engagement activities performed outside of the UK for multinational trials can considered in the same way as UK activity, where relevant.

3.2 Research Transparency

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 consulted on three proposals to increase transparency of clinical trials to introduce a requirement:

- to register a trial prior to its start,
- to publish summary of results within 12 months of the end of the trial, and
- to share trial findings with participants in a suitable format.

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

There were 2061 responses, of which

- 1994 (96.7%) agreed
- 47 (2.3%) disagreed
- 20 (1%) had no opinion

There was clear support for having registration as a legislative requirement, responses indicated this would enforce best practice by putting longstanding ethical requirements on a statutory footing, but there were questions over how this would be enforced.

There were many requests for the requirement to register a trial to be easy to fulfil, with easy-to-use websites, a single database, and clear guidance, and to consider automatic registration as part of the trial approval.

Those who disagreed questioned whether a legislative requirement to register a trial was suitable for all trial types and considered that this might be too prescriptive, increase paperwork and potentially cause unnecessary delays. Some responses highlighted that introducing any UK specific additional requirements might de-incentivise commercial trials in the UK. There were also some requests for a deferral option for commercially sensitive and phase 1 trials, as this would be in line with international requirements.

Government response
The vast majority of respondents were supportive of the proposal and therefore we will introduce a legislative requirement to register a trial in a World Health Organization compliant public register unless a deferral is agreed by or on behalf of the Research Ethics Committee.

Trial registration is already expected best practice and automated by the HRA as part of the approvals process. The legislative requirements will formalise this expectation and there is a clear consensus that it is important that trial participants and the public are aware of what trials are being conducted.

The responses have highlighted that clear guidance will need to accompany the provisions, including what registers are acceptable. It will also be important in the legislative drafting that the provisions are flexible to be appropriate for all types of trials, and to be considerate of international expectations. The legislation will also make provision for the possibility of exemptions, under exceptional circumstances, from the requirement where justified and agreed with the competent authorities, on a case-by-case basis.

Question 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?

There were 2062 responses, of which

- 1939 (94.0%); agreed
- 93 (4.5%) disagreed
- 30 (1.5%) had no opinion

A significant majority of responders agreed with a legislative requirement to publish a summary of results. There was support for a clear timeline and agreement that legislation was necessary to improve the rate of publication. It was considered that this would improve public trust in research, reduce duplication in research and ensure publication of negative findings.

Responses highlighted the need for a clear definition of 'end of trial' and clear guidance on what the summary should include, where it should be published, and support offered on how to write the summary in an accessible way. It was also highlighted that a requirement should not go beyond EU/USA requirements.

There were some concerns that a timeframe of 12 months was too short, especially for studies with issues of commercial sensitivity, where studies do not have a clear endpoint, and when factors outside of the trial team's control may make this impossible, whilst others considered 12 months was too long and summaries needed to be made available sooner.

There were mixed responses on deferrals, with many organisational responders highlighting that deferrals would be important, particularly in consideration of protecting commercially sensitive information or for certain types of trials. On the other hand, individual responders tended to disagree with deferrals or indicated deferrals should be time-limited, for instance 24 months with penalties for non-compliance.

Some responders considered that that this requirement should be included in guidance as legislation would create undue pressure or burden on trial teams to publish summaries quickly and so may result in errors. Some also felt that a requirement would not be suitable for all study types, and studies which may have no/negative results would be difficult to publish at all.

Government response

The majority of respondents were supportive of the proposal, and we will introduce a legislative requirement to publish a summary of results within 12 months of the end of the trial unless a deferral has been agreed.

Many responses felt that increased transparency would support scientific rigour, and evidence-based decision making, reduce the duplication of research and ensure that others can find out where no effect was observed or where findings were negative. We agree. It is imperative that all results are reported, which will promote better evidence-based decision making.

Reporting of results is already expected best practice. The legislative requirements will formalise those expectations and there is clear consensus that it is important that all findings from research are published. The legislation will also make provision for the possibility of exemptions, under exceptional circumstances, from the requirement where justified and agreed with the competent authorities, on a case-by-case basis.

We will publish comprehensive guidance that will cover definitions, the content of the summary, use of deferrals, and international expectations.

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

There were 2062 responses, of which

- 1878 (91.1%) agreed
- 114 (5.5%) disagreed
- 70 (3.4%) had no opinion

There was strong agreement with the proposal for a legislative requirement to share trial findings with participants. Many responses highlighted the need for participants to have access to findings as it encourages participation in the future, increases public confidence, and makes the participants feel valued. Some noted that it should be offered as a choice to participants in case they do not want the results, or to offer an option to provide findings to family members instead. There were some concerns around data handling, data protection and ensuring permission was sought to keep participant details for this purpose.

Guidance would be required on what needs to be communicated, when and how, and what to do in circumstances when a trial ends early or there are findings of no effect.

Those who disagreed highlighted that this would be better placed in guidance over legislation, noting that Research Ethics Committees already review how findings are shared. Some expressed concern about the additional burden for trial teams and considered that the decision

about communicating findings should be left to the trial team and patient and public involvement group for each individual study.

Government response

The majority of respondents were supportive of the proposal; therefore, we will introduce a requirement to offer trial findings with participants in a suitable format or explain why this is not possible.

Sharing findings with participants builds trust and incentivises patients and the public to participate in research. This requirement will make transparency of results reporting meaningful to patients and the public, and not a regulatory 'tick box' exercise.

The responses have highlighted that clear guidance will need to accompany the provisions, including where and when to communicate findings and what a 'suitable format' might look like. It will also be important in the legislative drafting that the provisions are flexible to be appropriate for all types of trials, and to be considerate of international expectations, whilst complying with data protection laws. The legislation will also make provision for the possibility of exemptions, under exceptional circumstances, from the requirement where justified and agreed with the competent authorities, on a case-by-case basis.

3.3 Clinical Trials Approval Processes

The consultation proposed several changes to update the process for approval of clinical trial applications, and to simplify and streamline processes. These included embedding the successful MHRA/research ethics committee combined review of trial applications into legislation with competitive timelines for review and increased flexibility to allow trial sponsors to respond to any questions raised.

3.3.1 Combined regulatory and research ethics approval

Question 5: Do you support a combined MHRA and ethics review of a maximum 30 days in general, with maximum 10 days for a decision following receipt of any Request for Further information 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.

There were 1390 responses, of which

- 930 (66.9%) agreed
- 238 (17.1%) disagreed

- 222 (16%) had no opinion

There was widespread support for the combined MHRA and ethics review, as responders thought that it would avoid any contradiction between the MHRA and Research Ethics Committee. However, it was also raised that in certain circumstances, such as where there were delays in selecting sites for some phase 1 trials, separate submissions should remain an option.

There was some concern that a combined review would mean that there would be no independent Research Ethics Committee opinion, or that MHRA would be taking on some of this responsibility, but this is not the intention of the proposal. There was also concern that the proposed timelines were for the overall completion of a whole clinical trial. We want to clarify that the question was about the time for the initial process to review an application to be able to run a clinical trial rather than the overall timeframe for the trial.

Multiple responses stressed that it was important to know whether the 10 days were calendar days or working days and feedback was received that the approval timeline should mirror the equivalent EU timeline so that the UK approach remains competitive. It was suggested that each step of the approval process should be clear in terms of timelines, including the initial validation of the trial application. Further to this, there were many comments which went beyond the consultation question, supporting legislating for the internal MHRA target of 14-days (not 30 days) timeline for initial review of phase 1 healthy volunteer trials.

Responders also highlighted that timelines for local Research & Development reviews, as well as other approvals (such as for Genetically Modified Organisms), still need improvement and there were requests for including other approvals beyond regulatory and ethics in the legislation.

Government response

Overall, there was clear support for the proposed timeframes for review of a clinical trial application, and we will take forward changes to introduce a combined regulatory and ethics approval process into legislation, but to keep the option for independent submissions available. We do not intend to align with the timelines set out in the EU regulation as these are significantly longer and less flexible than those we have proposed. We will implement a timeline for completion of an application review within a maximum 30 calendar days in general, with a maximum 10 calendar days for a decision to be granted once the regulator has received responses to any Request for Further Information.

The combined review process has been successfully trialled through a pilot since 2018 and has been the exclusive route for submissions since January 2022, so providing for this in legislation will cement a more streamlined application process for trial sponsors. Whilst the process for submitting application documentation will be streamlined, with a co-ordinated review, the regulatory and ethics reviews will still be performed separately by the MHRA and the Research Ethics Committees, ensuring robust and independent review of clinical trial applications but with the ability to collaborate and communicate as appropriate to ensure participant safety.

We recognise that setting up a clinical trial can require more than MHRA and ethics approval, for example approval from other regulators or from local trial sites. As part of the cross-system implementation of the UK vision for clinical research delivery, the UK Clinical Research Recovery, Resilience and Growth (RRG) programme will take forward plans to identify additional ways to simplify and streamline requirements (including costing and contracting), enabling inclusive, sustainable, data driven and digitally enabled studies to be done more quickly and easily. Phase two in delivering on our vision for clinical research will include plans to continue in streamlining processes, further strengthening our regulatory environment and ensure faster approval, set-up and delivery of studies with more predictability and less variation, particularly important for commercial contract research as driving our ability to attract global multi-centre research studies into the NHS.

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

There were 1389 responses, of which

- 897 (64.6%) agreed
- 224 (16.1%) disagreed
- 268 (19.3%) had no opinion

The majority of responders supported a proposed generous time period for a sponsor to respond to any requests for information raised (RFI) by MHRA and/or the ethics committee. The proposed period would be 'sponsor-driven' in that the sponsor would have the ability to respond very rapidly where appropriate, or to use the additional flexibility to allow them adequate time to develop robust responses to any questions.

Organisational responders suggested that RFIs could be done on a rolling basis rather than in a single letter, as included as a proposal in a later section of the consultation. There were also suggestions that there should be an option for submitting responses on a rolling basis too. Additionally, there were requests for trials to have a second round of RFIs, particularly for trials for advanced therapy medicinal products.

It was highlighted that a flexible extension should always be justified by the sponsors and should not be easily abusable, although some responses did express a wish for extensions to be easy to obtain. There was a desire for clear guidance on obtaining extensions, with an additional suggestion for the number of extension requests received to be published regularly. Responses also highlighted that extension requests could allow for aligning of multi-national protocols, which would reduce the resource needed.

There was a lot of reasoned discussion around the 60-day length of extension, with some suggesting that it is too long to be competitive and should be reduced to 30 days. Others thought that in some cases 60 days was needed, especially when the requested information needed to be obtained from third parties, such as when an academic sponsor needs information from a manufacturer.

Government response

There was overall support for this proposal and therefore we will introduce a 60-day timeframe (with flexible extension) to respond to any requests for further information. This flexibility will enable sponsors to prepare robust responses and interact with assessors to satisfy the regulators and avoid application rejections. We believe the flexibility afforded during the 60 days response time will mean that introduction of multiple rounds of RFIs will not be necessary and will keep the process as efficient as possible. It is important to note that the 60-day proposal is a maximum timeframe, so the sponsor could respond as quickly as they would like up to this limit. We will provide guidance detailing how extensions may be obtained.

Question 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.

There were 1389 responses, of which

- 924 (66.5%) agreed
- 240 (17.3%) disagreed
- 225 (16.2%) had no opinion

Overall, there was support for a combined MHRA and ethics decision with a timeline of 10 days from when the regulator and RECs receive responses to any Requests for Further information. Many agreed that 10 days would be a competitive timeline with the EU and would allow for an efficient approval process. Comments to this question focused mostly on whether 10 days was too short a timeframe and would require more resource. There was particular concern regarding REC members who are volunteers, where the apparent short timeframes may be more of a problem.

Government response

There was clear support for the proposal therefore we will introduce a combined MHRA and ethics final decision on a trial application of a maximum of 10 days following the receipt of any Requests for Further Information (RFI) responses. This timeframe has been piloted successfully in the MHRA and ethics committee combined review; however, we note the concerns raised and will consider appropriate flexibility in the legislation for additional time to reach a decision for the most complex cases.

Question 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?

There were 1390 responses, of which

- 1181 (85%) agreed
- 98 (7%) disagreed
- 111 (8%) had no opinion

There was clear support for regulators to have the ability to extend the assessment timelines in order to seek expert advice where the trial may present greater risks. Responses highlighted the need to very clearly define the risks that would trigger such an extension, along with clear guidance on the process and the timelines. Some responders raised concerns whether the extended timeline would be too long to be competitive with the EU (for similar cases where an extension is allowed to seek expert input).

It was suggested that it would be helpful to publish metrics for cases where such an extension had been deployed, particularly on the time taken for the review of each case.

Government response

This proposal was strongly supported, and therefore we will introduce the ability for the regulators to extend the timeframe for review of a trial application, where the risks to the participants may be greater, so that independent expert advice may be sought, noting the concerns that this extension should be in line with other international schemes.

It is clear that guidance will be needed, and we will produce clear and detailed guidance that addresses the highlighted need to define the types or trial or product for which extensions would be triggered.

MHRA already publishes metrics on clinical trials performance and will continue to do so. We will consider inclusion of cases for which an extension has been deployed in these metrics, but this will not form part of new legislation.

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

There were 1390 responses, of which

- 1058 (76.1%) agreed
- 194 (14%) disagreed
- 138 (9.9%) had no opinion

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

- Legislative change with the time limit specified in the legislation (267 – 25.2%)
- Legislative change with the time limit specified in guidance (111 – 10.5%)
- Legislative change allowing for exemptions if a good rationale is provided in the protocol and approved by the competent authorities (517 – 48.9%)
- No opinion (163 – 15.4%)

More than three quarters of respondents agreed that it would be appropriate for a clinical trial approval to lapse after a specified time if no participants have been recruited. Most considered

this would be best achieved through legislative change but allowing exemptions in the clinical trial protocol, subject to approval by the competent authorities (i.e., the MHRA and RECs).

Many of the responses to this question highlighted that exemptions need to apply in certain cases, such as in rare diseases where recruitment might be slow, or specific circumstances such as during pandemics. Guidance should be clear that there is a duty of care so that the sponsor ensures a trial remains fit for purpose if recruitment is slow. There were varying opinions on how easy it should be to attain an exemption, but it was commonly stated that the MHRA should be the ones to approve exemptions on a risk-proportionate basis. There was also support for an exemption to be possible upfront, agreed at the time of initial approval, if the trial protocol allowed for it.

There were also several responses, particularly from organisations, suggesting that we should consider allowing a pause to a clinical trial, where the approval remains valid, in addition to a lapse where the approval no longer is valid, and the trial should close. There were queries around how lapses will be monitored and the implications for the trial in the case of a lapse, questioning whether it means that a whole new clinical trial approval is needed if the trial sponsor wishes to continue the research.

Government response

There was clear support that the approval for trials in which no participants have been recruited should lapse after a specified period of time. This proposal will therefore be taken forward. Taking on board the comments received, we will ensure that the legislation provides potential for deferrals or extensions to the lapse time period, and a clear process is in place for how these can be requested and reviewed.

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

There were 1059 responses, of which

- 480 (45.3%) agreed
- 324 (30.6%) disagreed
- 255 (24.1%) had no opinion

There were mixed responses to the question of whether schedule 3, which sets out the particular documents that accompany an application, would be better placed in guidance rather than legislation. Overall, there was greater support for current schedule 3 granular detail to be in the form of guidance rather than in legislation.

Responses did highlight widespread support, however, for the core documents to remain listed in legislation, and guidance should just be for additional detail and other documents. This

would lead to clarity over the requirements and prevent unnecessary RFIs that ask for missing documents, which was considered by many as a more proportionate approach.

There were several concerns with the list of documents being solely in guidance, that it might be more difficult for sponsors to be up to date if guidance changes, it might lead to large deviation from EU Clinical Trials requirements, and it might lead to poor application quality.

Government response
Whilst feedback was mixed, the majority of responders were in favour of the detail in schedule 3 being in guidance rather than the legislation, and we plan to take this forward. Documentation is a critical part of any clinical trial, and we agree that core documentation (e.g., the trial protocol, IMP (Investigational Medicinal Product) dossier and investigators brochure) should be specified in legislation but that the current granularity in schedule 3 should be removed to allow 'futureproofing' and agility to respond to emerging innovation.

The responses have highlighted where guidance will be particularly important to ensure appropriate interpretation of the legislation, and provide support to sponsors, and these comments will be reviewed again when these elements are being drafted.

3.3.2 Requests for Further Information

Requests for Further Information are issued by the MHRA and/or Research Ethics Committees to a trial sponsor if a clinical trial application does not have sufficient information to allow an approval, or where changes to the submitted information is needed. The consultation made proposals to introduce greater flexibility to the formal communication between applicants and regulators during the process of requesting this information.

Question 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?

There were 1126 responses of which

- 794 (70.5%) agreed
- 165 (14.7%) disagreed
- 167 (14.8%) had no opinion

The large majority of respondents agreed that the proposal to have sight of Requests for Further Information (RFI) when they are ready would be advantageous. Some respondents commented that being able to have a dialogue with MHRA had been hugely helpful during COVID-19 and recognised that implementing a more interactive engagement across all trials would require MHRA to be resourced appropriately.

It was encouraging to note feedback that giving the opportunity to process RFIs when ready should help speed up the process to the benefit of the rare disease community. Feedback from members of the Phase 1 community expressed a view that early feedback is a “definite advantage” for Phase 1 trials where clinic schedules were often time sensitive.

Some concerns were raised about introducing complexity into the system by ‘drip-feeding’ information, which would be harder for sponsors and researchers to manage internally. Other concerns were that this process would introduce multiple timelines to respond to queries as they were raised.

Some respondents recognised that the proposal would have IT infrastructure implications and that any legislation to allow this should not dictate how this is achieved. Others expressed a view that the process may not need to be on the face of legislation and that the flexibility and process should be set out in guidance.

We acknowledge that the consultation document did not adequately explain the function of an RFI, this led to some responses expressing concern that these were issued post-approval, which is not the case. RFIs are issued prior to any regulatory or ethics approval of a clinical trial and questions raised must be resolved to the satisfaction of MHRA and/or the research ethics committee as appropriate *before* any authorisation is given.

Government response

The large majority of responses were in favour of this proposal and therefore we will ensure that legislation permits the trial sponsor to have sight of Requests for Further Information (RFI) as they are finalised per review discipline, rather than waiting for all reviewers to finish before issuing. We will consider whether the ability to sight sponsors on RFIs needs to be actively included in legislation or if the best course of action is simply ensuring legislation does not block this ability.

It is not the intention of the proposal to drip feed RFIs and the guidance to accompany this process will make it clear that RFIs will not be released ‘piecemeal’ or have different response times attached. The intention is that the legislation would not act as an impediment to allowing the sponsor to be sighted on RFIs as each discipline (ethics, medical, pharmaceutical or non-clinical) finalises their initial assessment of the application, for which the outcome will be an acceptance from that discipline or a list of RFIs that need to be addressed. This gives the sponsor the opportunity to review and begin to address these if they wish. The clock for the sponsor to provide their response to the request will only start when the final discipline has notified their initial assessment outcome and the full response to all RFIs should be submitted at the same time.

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

There were 1126 responses of which

- 855 (75.9%) agreed

- 100 (8.9%) disagreed
- 71 (15.2%) had no opinion

The proposal to receive an RFI during the review of a substantial amendment received a favourable response by a significant majority of responders. Responders highlighted the benefits of this approach in streamlining the current process and avoiding rejections that may cause delays or interruptions to an ongoing trial. This proposal was considered particularly helpful for advanced therapy medicinal product (ATMP) clinical trials and for complex/innovative trial designs where amendments may be more substantial than traditionally.

It was noted that while the proposal sought feedback on the ability to receive an RFI during an amendment, it did not include timelines for response, and that these should be included in the legislation.

Some respondents noted that most substantial amendments are approved on first review and the ability to issue a RFI should not mean that this becomes commonplace. Internal processes will also need to have an expectation that no more RFIs will be issued than the current rejection (or informal clarification) rate.

It was also noted that since a proposed amendment may never be acceptable to MHRA and/or the REC, the regulators should have the opportunity to refuse an amendment outright, rather than adding a redundant RFI step to the process. Respondents considered that the additional time to issue and respond to an 'unanswerable' RFI could be better spent moving on with the study as originally approved or to consider an alternative proposal.

In addition to responding to the question posed, some respondents welcomed and thanked the MHRA for the proposal 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.

Government Response

The large majority of responses supported this proposal, and we will therefore introduce an ability to receive an RFI during the review of a substantial amendment and legislation will include clear and competitive timelines for response and final decision. The legislation will also allow an outright rejection of an unacceptable amendment without an RFI step.

Introduction of an RFI step for amendments will include the ability for regulators to also reject a proposed amendment outright, where it is clear no further information would allow an approval.

For both questions in this section there will be further engagement opportunities with relevant stakeholders in the creation of the detailed guidance which will help to ensure proper interpretation and implementation.

3.3.3 Notification Scheme for Low Intervention Trials

The consultation proposed introducing a notification scheme for Low Intervention Trials into legislation. Low Intervention trials are clinical trials where the risk is similar to that of standard medical care. A similar scheme currently exists in MHRA guidance.
A notification scheme for Low Intervention Trials 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 full regulatory assessment, although an opinion from a research ethics committee would remain a requirement.

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

There were 1127 responses of which

- 834 (74.0%) agreed
- 160 (14.2%) disagreed
- 133 (11.8%) had no opinion

The majority of responders who answered this question agreed with introducing the concept of a notification scheme into legislation. Several responses took the view that the current regulatory assessment of low-risk studies was not required and can lead to unnecessary delays.

It was considered that introducing this proposal into legislation rather than the current guidance should increase confidence within the academic community to use this scheme. It was suggested that this approach would significantly reduce the risk averse culture among many public sector sponsors and reduce the regulatory burden of low-risk trials on participating NHS sites.

However, some respondents raised concerns over the potential for unintentional or intentional misclassification of the trial by sponsors and the apparent absence of regulatory oversight for these studies. Some also expressed concern regarding the transparency of these studies.

It was also questioned whether there would be any restrictions to the use of data generated from a trial authorised under the Notification Scheme.

Government response

There was significant support for a notification scheme, and we will introduce the scheme into legislation. Providing a clear legislative basis for the scheme will increase confidence in the use of the scheme, particularly within the academic community, reduce risk adverse culture among the public sector sponsors, and reduce regulatory burden.

While trials applicable for the notification scheme would undergo a proportionate assessment, there will be no relaxation of the new requirements outlined in this consultation response for the registration of the study and reporting of results. As set out in the consultation, notification scheme trials would not be excluded from Good Clinical Practice but are less likely to be selected in routine inspections based on the risk-proportional approach to selection of individual trials and organisations for inspection. Trials using the notification scheme would still require review by a Research Ethics Committee.

Question 13b: If yes, do you agree that the subset of trials outlined would be appropriate to be eligible for a notification scheme?

The consultation included a definition of a low intervention trial based on that from the Organisation for Economic Co-operation and Development (OECD), the European Union, and MHRA definitions for risk stratification. This was: *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*. Some respondents considered that the OECD definition of a 'low-intervention trial' is insufficiently broad and there was support for the consultation proposal not to exclude placebo-controlled trials from the Notification Scheme.

Several responses requested that the MHRA further engage with stakeholders to establish an appropriate definition that facilitated low risk clinical trials without undermining patient safety.

A number of respondents also suggested that there should be a feedback mechanism for the MHRA to inform sponsors of eligibility for the Notification Scheme for applications submitted for assessment. This would allow the MHRA to reclassify the trial as 'low intervention' at any point during its journey from submission to authorisation. However, use of the Notification Scheme for eligible trials should not be mandatory so as not to impact on international collaboration, where a trial is also being conducted in a country without a procedure equivalent to the Notification Scheme.

Further, a suggestion was made that it would be beneficial to build in a legislative mechanism to allow long-term follow-up of clinical trials (e.g., through linkage to routine healthcare data or periodic patient questionnaires) to be reclassified as low-intervention or non-intervention once the main treatment comparisons have been completed. This is addressed in a proposal later in the consultation.

Government response

The consultation responses reflected that the scope of the notification scheme proposed was broadly acceptable. We intend to introduce the concept of the notification scheme and the definition of a low intervention trial into legislation but set out clear eligibility for the scheme in guidance. Eligibility for the Notification Scheme will be restricted to clinical trials in which the risk to trial participants is considered no greater than that of standard clinical practice. Although exact eligibility requirements are yet to be fully defined, it is likely to be restricted to a subset of trials involving licensed products used either within their licensed indications or where there is established clinical practice.

This scheme is intended to embed more risk-proportionate approaches into the conduct of clinical trials, considering the widely varying level of risk associated with different clinical trials. For example, a clinical trial that is evaluating established clinical practice or is being conducted using a marketed product, such as aspirin, presents a much-reduced level of risk compared to a trial investigating an entirely new chemical or biological entity. It is appropriate that trials where the medicine under investigation is already proven to be safe in the population being studied, do not require the same level of regulatory review. Research Ethics review will still be required.

A clear definition of trials eligible for the Notification Scheme will be developed in collaboration with patients, researchers and trial sponsors and published in guidance, to accompany the legislation. This will also consider the operation of the scheme and the possibility of including a feedback mechanism and classification of long-term follow-up trials.

Question 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?

Due to a technical issue with the online survey very few responses to this question were received. However, written responses did address this question.

A small number of respondents were concerned that high-risk clinical trials may be authorised under the Notification Scheme without appropriate regulatory oversight.

Government Response

An appropriate level of oversight for these trials will be maintained through Research Ethics Committees. Risk proportionate Good Clinical Practice requirements, as well as the possibility of inspection by the MHRA, will be maintained for all trials, including those authorised under the Notification Scheme, to ensure that trials are being conducted appropriately. The requirement to register and report results for these trials will also remain. Any trials identified as not being eligible for the Notification Scheme will be referred to the standard MHRA authorisation process and the regulator will have the ability to liaise with the sponsor where their study is eligible for the notification scheme but submitted for standard review and allow reclassification where appropriate.

3.4 Research Ethics

Research ethics reviews safeguard the rights, safety, dignity and well-being of those participating 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 consultation proposed to update requirements for the make-up and minimum number of members of Research Ethics Committees (RECs) and remove restrictive and granular requirements such as for premises and facilities and refer to guidance to allow for greater agility in decision making.

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

There were 844 written comments in response to this question. The general consensus was that REC membership should consist of a good cross-sectional make-up to include a breadth of working professional clinical expertise. Research and statistical expertise was also considered essential within the REC membership to provide strong analytical skills to facilitate effective REC work, alongside patient representatives. There were a number of requests that the REC members should not have any commercial or pharmaceutical conflicts of interest and must be appropriately trained, for example in research methodology and that training should be documented.

There were several suggestions that very clear definitions of expert and lay person were necessary, and that guidance would be needed to support any legislation changes. Comments encouraged unified guidance being adopted by all RECs in the UK to ensure consistency and a one-rule fits all approach, even if the rules are provided in guidance rather than legislation.

A minority of responses considered that the granular detail outlined in Schedule 2 of the legislation should not be deleted because RECs have been proven as safe and robust and the current legislation has been effective and removing the exact legal requirements could lead to a watering down of standards over time. It was also noted that any changes in RECs would need to meet internationally expected requirements.

Government response

The responses demonstrated support to include a cross-sectional make-up of members as outlined in the consultation document and therefore we will proceed with this proposal.

Legislation will refer to key principles around membership constitution, quoracy and training. Guidance will be used to set out detailed definitions to avoid current problems resulting from legislation using out of date terminology. REC membership will continue to meet internationally expected requirements.

We plan to continue with our proposal to delete schedule 2 of the current legislation. We agree with comments that RECs are safe and robust; however, we do not believe that legislating, for example, for the administration, maintenance and cleaning of facilities where the committee meets contributes to this, and therefore we will refer to HRA policy and guidance in these matters. Similarly, although we will include principles about the cross-sectional make-up of members, we will not include detailed professional roles or organisational affiliations as currently included in the schedule, because these can become out-dated.

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

There were 1288 responses of which

- 662 (51.4%) agreed
- 491 (38.1%) disagreed
- 135 (10.5%) had no opinion

There was clear appreciation that patients are diverse and clinical trials should appropriately represent the wider population. Across all responses there was broad agreement on the importance of raising awareness of improving diversity in clinical trial populations and to encourage and support research teams to take equality and diversity into consideration when designing studies.

The question of whether legislative requirements should be introduced to support diversity in clinical trial populations gained a mixed response, and there were differing opinions between organisations and individual responders. Of the organisational responders 40% answered yes (80 out of 202 organisational responders), whilst a larger proportion of individuals, 61%, said yes (582 out of 951 individual responders).

Many were concerned to avoid a requirement for diversity in all situations since it may not be safe or ethical to include a completely diverse population in every trial. It was considered that issues of risk, need and benefit are not equal across different patient/ participant groups and consideration should be given to participant inclusion based on a clear assessment of risks and potential benefits specific to different population groups in different trials. Particular concerns were raised around the risks of certain trials to people who are pregnant or in certain age groups. It was suggested that guidance might be more effective at addressing these issues than legislation.

Other responders suggested that it would be advantageous for certain demographics to enter trials and that equity through diversity is key for better understanding of the communities we serve. RECs should be empowered and enabled to make informed judgements and decisions about whether applications sufficiently justify inclusion / exclusion based on need and the potential risks and benefits.

There were significant concerns that introduction of a legal requirement for diversity in clinical trial populations may prevent trials happening, as there are circumstances where diversity may not be possible, such as in single-site trials in non-diverse locations, or trials focusing on a specific ethnic or socio-economic group. It was also considered that a legal requirement may limit recruitment to trials, and this may be seen by sponsors as a reason to look for participants outside of the UK.

It was suggested that more research is needed into why participants in early phase studies are not as diverse as needed, which would then inform the intervention needed, and legislation introduced if non-legislative means did not have the expected result.

Government Response

There were mixed views on this question, there was clear appreciation from responders that trials should represent the wider population, with a small majority in favour of introducing legislative requirements. Having considered the balance of opinions, we will introduce explicit guidance on diversity to ensure populations in trials are representative rather than a new legislative requirement. Patients are diverse and it is important that clinical trials fully represent the population affected by the specific disease or condition that is being studied, to assure that the medicine under trial will be safe and effective for all patients who may later receive it in the wider population. For example, ensuring balance of sexes, population groups and participants of different ages, as appropriate to the condition being addressed, will help tackle health disparities and give the best and most reliable results from the study to the overall benefit of all patients across the UK.

A considerable amount of work is already underway on a non-legislative basis, with different organisations providing frameworks, training and toolkits for researchers, and initiatives to increase diversity within clinical trials are included in many strands of the UK Clinical Research Recovery, Resilience and Growth (RRG) programme.

Introducing further guidance will ensure that researchers understand how to achieve diversity in their trials in a manner that is proportionate and achieves the best results. Guidance will make clear the expectations for trial sponsors to appropriately consider diversity in trial populations to encourage wider representation in trials. Taking this approach through guidance rather than legislation will ensure the flexibility necessary to reflect the many different types of clinical trials and participant populations, and avoid any unnecessary risks or constraints related to unforeseen disease burden, evolving views on how to define diversity and new technologies and trial designs. For example, guidance will set out considerations of risk and benefit of trials when designing inclusion and exclusion criteria to address concerns raised about people who are pregnant or in certain age groups or in particular risk groups.
There will be further engagement opportunities with relevant stakeholders in the creation of this detailed guidance to ensure proper interpretation and implementation.

3.5 Informed Consent in Cluster Trials

Cluster trials are one of the ways to perform large-scale randomised controlled trials to compare different available treatments and observe which is the most effective. 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 one medicine and all participants in another hospital would receive another medicine.

The consultation made proposals to simplify the way that informed consent can be obtained for cluster trials to promote support greater use of these kinds of trials. The proposal was that 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.

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.

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

There were 1181 responses of which

- 724 (61.3%) agreed
- 379 (32.1%) disagreed
- 78 (6.6%) had no opinion

There was a mixed response about whether the legislation should enable flexibility on consent provisions where the trial is considered to have lower risk. However, the majority of responders who expressed an opinion on this question supported the proposal, 61% of individuals (565 out of 923 individual responders) and 88% for organisations (157 out of 178 organisational responders).

A majority of comments highlighted that consent should be fully informed, there was a clear expectation that all risks should be clearly explained to participants. Many responses raised concern that with flexible consent provisions, participants may be unaware of what is being investigated and what alternative options are available. However, other comments considered the proposal would be beneficial and suggested that it should be extended beyond observational trials, to also include other kinds of trial designs that are also lower risk.

There were many requests for clear guidance and definitions, to ensure clarity on what would be required and the different consent options available. It was considered this guidance should be developed with suitable patient and public involvement to provide flexibility whilst also continuing to provide assurance on safety.

Government response

The majority of responses agreed with the proposal and therefore we will proceed to enable flexibility on consent provisions where the trial is considered to have lower risk.

Guidance will be developed alongside the legislation to support flexibility on consent provisions in trials that are considered to have lower risk. This guidance will be developed in collaboration with stakeholders, including patients and the public, to ensure that any flexibility introduced into how consent is sought and documented does not compromise the ability of potential participants to provide adequately informed consent to taking part in clinical trials.

Question 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?

There were 1181 responses of which

- 766 (64.9%) agreed
- 336 (28.4%) disagreed
- 79 (6.7%) had no opinion

Responses were supportive of the proposal but were clear that any simplification must still result in patients being able to make a fully informed choice. There was an overwhelming view that risks should be clear to patients and that they should have a right to opt out of any trial. Patients must be aware of the health service they are accessing and if necessary, they have the choice to have the alternative treatment, without additional costs.

Responders highlighted the importance of data protection, noting that anonymity should be maintained, and General Data Protection legislation requires a valid lawful basis for the processing of personal data.

Government response

The majority of responses agreed with the proposal and therefore we will proceed with the proposal for cluster trials comparing existing treatments to use a simplified means of seeking consent from participants. The proposal will comply with all UK Data laws. Clear guidance on consent requirements will be developed to support the legislation and guidance to ensure that simplified consent is understood.

3.6 Safety Reporting

The consultation proposed updates to the pharmacovigilance aspects of clinical trials, aimed at reducing administrative burden while maintaining the highest standards of participant safety.

Sponsors of clinical trials need to identify Suspected Unexpected Serious Adverse Reactions (SUSARs), these are serious adverse events suspected to be caused by the medicinal product under investigation. These must be reported in an expedited manner to the MHRA on an individual basis. We proposed to remove the legislative requirement for sponsors to directly report SUSARs to investigators and Research Ethics Committees (RECs) because there are other ways both investigators and RECs can receive this information. We also proposed that sponsors should be allowed to assess the causality of some serious adverse events through reviewing cumulative data rather than single occurrences.

Sponsors also have a legal requirement to submit annual reports containing safety information about the medicine under investigation. The consultation proposed these are sent only to the MHRA, rather than also being sent to RECs, because it is the MHRA's responsibility to monitor

the safety of ongoing clinical trials. MHRA would then liaise with the REC as necessary if any action was required. Sponsors currently provide a list of every individual serious adverse event and reaction in an annual safety report. We proposed the alternative approach of providing a discussion of the signals/risks identified during the year, to improve the quality of the information provided, since a robust discussion would help understand the most meaningful events.

We also proposed that where sponsors and/or investigators take urgent safety measures to protect the safety of trial participants they should have a maximum of seven, rather than three, days to inform the MHRA in writing, to align with the timeframes internationally.

Question 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.

There were 1213 responses of which

- 500 (41.2%) agreed
- 561 (46.2%) disagreed
- 152 (12.5%) had no opinion

Opinion was mixed on the proposals to remove the requirement for individual SUSARs to be reported to all investigators. Those who did agree with the proposal considered that aggregate data in the Investigator's Brochure (the document that contains a summary of the data about the medicine being investigated) may be more informative for investigators than SUSARs received in isolation.

A key theme throughout responses was concern that the proposal would limit the access of investigators to relevant safety information in real time, particularly in early phase trials where prompt decisions need to be taken regarding whether to halt dosing.

Some responders wondered how investigators would receive safety information in trials where the trial conduct is supported by Summary of Product Characteristics (SmPCs) rather than IBs and the trial sponsor is not the marketing authorisation holder. There was concern that the trial sponsor would have no control over the SmPC updates, but also that the updates do not occur at regular intervals of time.

It was also felt that the proposed changes could reduce international harmonisation particularly with the clinical trial legislation in the European Union.

Government response

Currently sponsors must inform regulators of SUSARs as and when these occur in an expedited manner. Investigators do not receive SUSARs in an expedited manner. They receive lists of blinded SUSAR reports. This is necessary to protect the trial integrity.

Responders were concerned that removing the requirement for sponsors to report SUSARs to investigators would reduce investigators real-time knowledge of ongoing safety concerns. However, this is not the case since there are other ways investigators receive safety information. While many of the responses disagreeing with this proposal may have been based on a misunderstanding of the current procedure, we have learnt that the current requirements are not clear enough. We will implement this proposal, but responses have demonstrated that we need to provide greater clarity and we will do so in clear guidance documents to accompany legislative changes.

Removing the legislative requirement for individual SUSARs to be reported to all investigators will not prevent sponsors from doing so if they choose to, but it will remove a duplicative legislative requirement, because investigators will still receive safety information in other ways. Investigators receive regular updates about the safety profile of the medicine as part of the Investigator Brochure. Sponsors can also send Dear Investigator Letters to the investigators. These letters communicate important information in a prompt manner.

For early phase trials safety is ensured not via SUSAR reporting to investigators, but through predefined halting or stopping rules listed in the trial protocol and approved by the regulatory authority before the trial commences.

For trials that use SmPCs or where the trial sponsor is not the owner of the Investigator Brochure (e.g., academic trials using a medicine that is already marketed), the trial sponsor will maintain the oversight of the trial and will need to communicate to investigators any significant changes to the safety profile of a licensed medicine which will have an impact on the trial conduct. Urgent safety measures, substantial amendments of the trial documentation, as well as Dear Investigator Letters can be used to achieve this goal. Concerns were raised about the sponsor's responsibility for the investigator's brochure. We will review the regulatory requirements to ensure that they do not cause undue burden on academic sponsors who do not 'own' the investigator brochure or SmPC for the product they are investigating.

We do not consider that this proposal risks reduction in international compatibility, since it is consistent with the EU Clinical Trials Regulations.

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

There were 1214 responses of which

- 561 (46.2%) agreed
- 493 (40.6%) disagreed
- 160 (13.2%) had no opinion

A small majority of responders supported the proposals to remove the requirement to report SUSARs and annual safety reports to Research Ethics Committees, because reporting to RECs is considered an added burden that does not improve the safety of trials, since it is the MHRA's responsibility to review accumulating safety data from ongoing trials. People in favour of the proposal considered that the MHRA should continue to receive safety reports and appreciated that the MHRA would be able to identify those cases where exchange of information with RECs is warranted. Those responders who did not support the proposals and preferred to maintain reporting to both the MHRA and REC, considered that the RECs act as an authority that is independent of the MHRA and add another level of control.

Government response

Overall, there was support for removing the requirement to report SUSARs to RECs, and we will implement this change. Responses demonstrate agreement that doing so will reduce the administrative burden while maintaining adequate safety oversight. The MHRA and RECs fulfil different roles in the oversight of clinical trials. The MHRA is responsible for reviewing ongoing safety information for clinical trials including the information contained in both SUSARs and annual safety reports, whilst RECS are responsible for the ethical considerations of the trial. By implementing this proposal, the MHRA will continue to receive this information and will continue working closely with RECS to ensure that the appropriate information is shared where necessary.

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

There were 1214 responses of which

- 562 (46.3%) agreed
- 448 (36.9%) disagreed
- 204 (16.8%) had no opinion

There was support for the proposal to enable SUSARs to be reported to the MHRA in an aggregate manner. The majority of responders agreed with the proposal because they considered that when trial populations have an expected high mortality rate or several co-morbidities it could be difficult to decide whether a single serious adverse event is caused by the medicinal product under investigation or by the natural course of the disease. Aggregate reporting could give a clearer picture regarding this.

While several responses indicated that reporting SUSARs in an aggregate manner could go against international harmonisation, some organisations thought it ensured alignment with existing initiatives such as the FDA Final Rule for Aggregate Reporting for human drugs and biological products.

The responses did draw out a number of concerns:

- Concern that this requirement would be mandatory and prevent identification of safety issues requiring urgent actions
- Concern that aggregate reporting would be an added burden, particularly for non-commercial sponsors, in terms of both human and financial resources due to the need of having adequate expertise and establishing independent data monitoring committees (IDMCs) for all trials
- Guidance should be provided regarding when aggregate reporting can be considered appropriate
- Need for clarification of the requirement of a system aimed at periodically reviewing accumulating safety data

Government response

There was a small majority in support of this proposal, and we will enable SUSARs to be reported in an aggregate manner. The comments received suggested that there was not enough clarity, and this led to a variety of misunderstandings, which we will address in detailed guidance documents to accompany the legislation. In line with current pharmacovigilance procedures, it is already possible to exclude some reactions from expedited SUSAR reporting in order to protect trial integrity. In addition, aggregate reporting will facilitate the assessment of links between adverse events and the medicine, that cannot properly be evaluated on an individual basis. For example, this will help better understand serious adverse events occurring in patients with several co-morbidities where it is difficult to distinguish whether the event is related to the study drug or to one of the conditions the participant suffers from.

Aggregate SUSAR reporting will not be mandatory and therefore will not be an additional burden. The intent is for the legislation to enable the option of reviewing some serious adverse events in an aggregate manner and this will only be acceptable if pre-specified criteria (which will be clearly defined in guidance) are met. Introducing a legislative requirement that trial sponsors must have a systematic approach for safety surveillance will ensure that they have the capacity to evaluate accumulating data and identify safety signals. In doing so sponsors can be assisted either by an Independent Data Monitoring Committee (IDMC) or by a safety team within the sponsor's organisation. This proposal promotes international harmonisation, for example the FDA requires that some adverse events are reported in aggregate rather than as individual cases.

Question 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?

There were 1214 responses of which

- 380 (31.3%) agreed

- 660 (54.4%) disagreed
- 173 (14.3%) had no opinion

Most responses, across both individuals and organisations, disagreed with the proposal to remove listings of serious events in annual safety reports. The main concern was that the removal of the listings would reduce transparency and introduce a deviation from the international standards described in the International Council for Harmonisation (ICH) 2EF guidance on the Development Safety Update Report.

On the other hand, some responders did agree with the proposal. These responders considered that lengthy line listings in the absence of a clear description of emerging safety signals and mitigation proposals are neither transparent nor provide meaningful information. It was also suggested that it may be worthwhile to elevate this topic for ICH discussion to investigate whether ICH members were in favour of updating the ICH 2EF guidance taking into consideration the MHRA proposal.

Government response

We will remove the legislative requirement to include individual listings of adverse events and reactions in annual safety reports. However, sponsors will still have the option to include the listings in their annual safety reports if they chose to do so. This will enable sponsors who prepare global reports that include individual listings to submit those to the UK competent authority, while other sponsors can reduce the administrative burden.

Sponsors prepare safety reports on an annual basis to reassure the regulators that they have adequate oversight of the safety profile of the investigational drug. However, the reports currently submitted to regulators are not transparent because they contain listings of all individual serious adverse events and reactions without a description of how they have been evaluated and interpreted.

The proposal to request that trial sponsors describe how safety concerns have been assessed and managed will increase the transparency of the annual safety report. The increased quality of the information included in the report will facilitate the regulatory review process, reduce additional requests of information from the regulatory authorities and ultimately demonstrate that the investigational drug is used in a safe manner. In addition, the regulatory authority would still be able to require that listings were provided if deemed necessary to investigate specific safety issues. The request to provide a discussion of the risks as well as the proposed mitigation strategies is consistent with the guideline already published jointly by the MHRA and Health Canada as well as expectations in the EU.

Question 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?

There were 1212 responses of which

- 602 (49.7%) agreed
- 400 (33%) disagreed
- 210 (17.3%) had no opinion

Most responders were supportive of the proposal to extend the written notification for Urgent Safety Measures (USM). Some responders were concerned that the extra days would result in delaying implementation of appropriate actions to protect the safety of the trial participants.

Those responders who did agree with the proposal, considered that the extended timelines would not only allow trial sponsors to collect relevant information, but also ensure international harmonisation.

Government response

The majority of responders agreed with the proposal, and we will extend the timeline for written notification of Urgent safety measures to 7 days.

Patient safety was the primary concern raised. However, extending the timeline for written communication to the regulatory authority will not jeopardise the safety of the trial participants. USMs are reported to the MHRA after they have already been implemented and actions have been taken to protect the safety of trial participants. The proposal is to increase the time to provide written notification to the regulator of those measures that have already been taken. The added time for written notification of the measure taken can be used to gather data that will facilitate the regulatory assessment of the measures. In addition, this proposal supports international harmonisation because similar measures are in the European legislation.

We will clarify in the legislation that the measures should be reported within seven calendar days of when they were taken. We will specify in guidance how to contact the MHRA and whether a phone call is still required.

Question 24: Do you agree that the proposed safety reporting requirements reduce burden on researchers but maintain strict levels of safety oversight?

There were 1213 responses of which

- 493 (40.8%) agreed
- 463 (38.2%) disagreed
- 255 (21%) had no opinion

There were many comments welcoming the changes to safety reporting requirements because they encouraged a risk-proportionate approach while safeguarding participant safety.

Responders highlighted that patient safety should not be seen as a burden. There was disparity of opinion regarding whose burden was reduced. Some thought that the proposed changes would reduce the burden of investigators but may increase the burden of sponsors by creating UK-specific requirements such as aggregate SUSAR reporting and absence of listings in the annual safety reports. Others were concerned that the sponsor's burden was reduced at the expense of appropriate safety oversight.

Government response

Across the safety reporting proposals, responses highlighted the clear need to identify and act on safety concerns quickly, to ensure that those involved in running trials are aware of emerging risks and that regulators have the necessary oversight. The safety of trial participants is paramount. The current legislation contains some reporting requirements that are duplicative or do not provide additional value in identifying safety risks. It is these aspects, as outlined in responses to each of the separate pharmacovigilance proposals, that we will address in the legislation. This will ensure that important information on safety is reported in the way that is most valuable to understand the risks, that unnecessary administrative burden is removed while maintaining the necessary oversight to assure safety of participants.

3.7 Good Clinical Practice

Good Clinical Practice (GCP) are the ethical and scientific quality requirements for designing, conducting, recording and reporting clinical trials. The UK legislation mandates compliance to the principles of GCP. Researchers follow these requirements to ensure that participants are safe, that the results of the trial can be relied upon and to inform the risks associated with the conduct of clinical trials. Every clinical trial is associated with a different level of risk. For example, there is a big difference between trials of new chemical entities, or an advanced therapy being used in people for the first time, compared to trials of licensed medicines used within the terms of a marketing authorisation. Processes associated with an individual trial can be adapted in line with any identified risks to the participants or to the overall reliability of the trial results, either increasing controls associated with particular areas or removing constraints where risks are considered low. The consultation proposed several updates to introduce in legislation the ability to consider the different levels of risk when considering clinical trial practices.

Question 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?

There were 1149 responses of which

- 826 (71.9%); agreed
- 204 (17.75%); disagreed

- 119 (10.35%) had no opinion

The majority of responders agreed that the current legislation was not proportionate to risk and the introduction of sensible proportionality into the legislation was welcomed. It was considered that trials focusing on what matters in terms of risk, rather than taking a uniform approach would be more efficient, reducing burden, and making better use of resources. In turn, responders felt this would encourage more research and innovation in trial design.

A key priority from responders was to ensure that any UK legalisation was also compatible with international standards, with some stating that the UK should implement and comply with international standards such as the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Good Clinical Practice (GCP). Responders noted that this international guidance was also being updated to include further risk proportionality. There was some concern that if the UK was not internationally aligned, there may be less selection of UK sites to participate in global trials and conducting international trials would become more difficult.

Comments suggested risk-proportionality would be more helpful to academic trials and those using licensed medicines, as the focus of these trials is commonly on extending the uses of products with a known safety profile, rather than the introduction of new medicines, and therefore can be of lower risk.

Those who disagreed with the proposal raised concern that risk-proportionality would reduce standards and increase risk to trial participants by providing an opportunity for 'cutting corners' and inappropriate proportionality assigned. There were also concerns about who was deciding and reviewing proportionality assessments. Many felt that the current legislation was robust and should be maintained or even made stricter to ensure the same standards apply to all trials. There were several comments that the focus should be on the trial participants and ensuring that risks are minimised for these rather than facilitating researchers in conducting the trial. These and other comments indicated the need for independent oversight and transparency of trial conduct.

A substantial number of comments highlighted the need for further detailed guidance and trial examples/case studies, alongside a desire for detailed definitions and clarity of what is allowed, and for this to be developed with stakeholders to encourage the adoption of the approach. Comments were made on the myriad of ways of conducting risk assessments and lack of a standard approach. It was suggested that risk assessment should be submitted to the MHRA to avoid the responsibility falling fully on the sponsor.

Government response

Considering the support, we will introduce greater risk-proportionality into the legislation. We will introduce an overarching expectation for sponsors to identify and document the risks to patient safety and the reliability of the data, and to apply proportionate controls. For example, this could include considering how the trial can be adapted to minimise the burden (arising from both the administrative and practical conduct of the trial) for all participants including

patients, investigator site teams. This will support the development of efficient and effective practices for trial delivery and conduct.

A significant number of requests were made to maintain harmonisation with international standards. The implementation of risk proportionate approaches is part of international standards and has been in progress for a number of years, including by the MHRA, EMA and ICH, therefore its implementation can be successful and consistent with international approaches.

A proportionate approach to trials is implemented by a clear risk and thorough assessment and effective risk management. Areas of risk to trial participants and the reliability of the trial results are mitigated and adaptations to GCP are only applied where these do not put the trial participants or the integrity of the data at risk. Risk assessments and compliance with GCP are reviewed during MHRA inspections and associated compliance activities. The MHRA will continue to oversee that effective standards are maintained to protect trial participants and the reliability of the trial results.

Experience of risk adaptations seen in practice tend to focus on administrative changes. The organisation must be able to justify the adaptive measures being implemented, must be able to mitigate any risks that are identified and to revisit the risk assessment whenever changes to the trial are made or if issues occur to ensure that it remains fit for purpose. As such, risk-based adaptations tend to increase oversight of patient safety and trial data rather than put it at risk.

Whilst the MHRA has already published guidance on risk-proportionality the responses highlight a clear need for this to be reviewed again, we will do so working with stakeholders, to encourage further adoption of the approach. We will also consider how best to improve ways of disseminating and training in this guidance and the risk proportional approach. The legislation and associated guidance for implementation will help encourage the adoption of risk proportionate approaches by both trial sponsors and regulators alike ensuring pragmatic adoption of risk proportionality in clinical trials.

Question 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?

There were 1149 responses of which

- 977 (85%) agreed
- 69 (6%) disagreed
- 103 (9%) had no opinion

There was a high level of support for ensuring electronic systems, such as those used for the generation, collection and management of clinical trial data and those used to provide trial management or randomisation capabilities, follow the principles of GCP. It was considered important that electronic service providers understand the impact of their systems on the ability

of sponsors to conduct a clinical trial, and several responders had experienced difficulties in getting electronic service providers to comply with GCP. Clear expectations for compliance with GCP could also assist in the selection and oversight of electronic system vendors.

A significant number of comments reiterated that the requirement should focus on electronic systems that impact participant safety and reliability of results and should not apply to systems that were not specifically designed for research activities (e.g., electronic health record systems used by the NHS). Several responses queried the feasibility of the proposal in terms of how this proposal would be implemented and the ability and experience of the MHRA to undertake detailed review of electronic systems.

Responders highlighted the need for electronic systems to be fit for purpose based on the requirements of the trial sponsor, and queried whether risk mitigation or other methods of sponsor oversight could be used if existing systems were not fully GCP compliant, especially where the systems could not be retrospectively modified to achieve compliance with GCP. This approach was also supported by requests for risk proportionate adherence to GCP for electronic systems. It was also requested that the responsibilities between sponsors and service providers relating to the provision and operation of outsourced systems be defined.
It was considered that care should be taken not to stifle innovation and development of electronic systems or to impact on the adoption of electronic systems within clinical trials either by preventing use of non-compliant systems where alternatives do not already exist or by imposing additional financial burden for the conduct of trials to support the acquisition of compliant systems.

Requests were made for the development of industry standards for electronic systems impacting on patient safety and data integrity, and for the introduction of certification of such systems by the MHRA.

Government response

We will explicitly state in legislation that electronic system providers will be required to comply with GCP regarding the provision, operation and management of systems used for the generation, collection and management of clinical trial data and those used to provide trial management or randomisation capabilities. We will ensure clarity that the focus of the requirement does not impact the provision of routine health care.

Electronic systems can have a direct impact on patient safety, data integrity and compliance with clinical trial protocols. The MHRA has been inspecting providers of electronic systems to ascertain compliance with GCP and regulatory requirements for over ten years, but the expectation for compliance is not currently clear in the legislation. Making this requirement explicit in legislation will ensure such systems operate to appropriate standards, to better support safe and effective clinical trials.

It was very clear from the responses that, in addition to the introduction of legislation to support this proposal, there is a need for additional guidance to support electronic vendors, investigators, laboratories and trial sponsors in understanding regulatory and best practice expectations regarding the complete lifecycle of electronic systems used in the conduct of clinical trials. We will develop this guidance to accompany the legislation.

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

There were 1149 responses of which

- 668 (58.1%) agreed
- 198 (17.2%) disagreed
- 283 (24.6%) had no opinion

There was general support for updating the GCP principles to incorporate risk proportionality. A proportionate approach to GCP principles was considered to encourage innovation, increase participation in trials and focus resources on the risks that really matter. There were comments that a one size fits all approach has not been appropriate and that a proportionate and pragmatic approach would be beneficial. It was highlighted that any changes made should be to the benefit of trial participants and that the changes must not compromise safety.

A significant number of responders stated that compliance with international standards was required, particularly ICH GCP, and that the current principles were acceptable and allowed proportionality already. Some respondents, both supporting and opposing the proposal, explicitly stated that a set of UK specific standards should not be implemented. There were concerns raised that the UK not being consistent with ICH GCP could compromise the global acceptability of UK clinical trial data for marketing authorisations and potentially reduce the number of commercial trials being conducted in the UK.

Some responders suggested that how the GCP principles are interpreted in practice can be an issue, for example in terms of the documentation expected. Many suggested that further guidance around risk and interpretation of what proportionality looks like in practice should be provided.

Government response

Considering the responses to the consultation proposals, we will include specific reference to the ICH GCP principles in the legislation. The adoption of the ICH GCP principles (which are currently undergoing revision) will support risk proportionality within the legislation as the draft principles clearly state the requirement that clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results. This will also ensure that UK trials continue to be conducted to internationally accepted standards, and the data generated in the UK can be accepted globally. The MHRA is a member of ICH and is closely involved in the development of the GCP standards.

ICH GCP is an international standard for the design, conduct, safety and reporting of clinical trials, that facilitates the mutual acceptance of clinical data across international regions. ICH GCP is composed of two parts, the GCP principles and detailed guidance. The principles are high level and are designed to be flexible and applicable to a broad range of clinical trials. The guidance is significantly more detailed and describes the responsibilities and expectations of all participants in the conduct of clinical trials. Together the principles and detailed guidance

form the international standard for clinical trials of medicines to support marketing authorisation applications. A trial that is not intended to be submitted to support a marketing authorisation application is not required to comply with all the requirements of ICH GCP.

We will only require compliance with the ICH GCP principles and will not mandate compliance with the entire ICH guidance. This will ensure the right balance of compliance with the core principles and flexibility for the principles to be applied proportionately to the specific trial. We will provide accompanying UK specific guidance on how to apply the ICH detailed guidance for trials for marketing authorisations and other trials, such as academic trials, that are not intended to support a marketing authorisation, based on a risk assessment of the trial. This will ensure compliance with international standards, including the addition of risk proportionality, and support the ICH GCP principles being adopted proportionately in the UK, depending on the kind of trial being carried out. It is important that clinical trial data generated within the UK is accepted by other global regulators as providing equivalent protection to patient safety and integrity of the data, to ensure continued UK involvement in international trials and collaborations.

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

In response to what GCP principles are important to remove or include, responders overwhelmingly supported retention of the existing principles, irrespective of whether they supported the earlier question on proportional GCP principles.
Many comments did not relate directly to the principles currently set out in the legislation and some referenced the ICH GCP principles. Many comments did not specify principles to include or remove, but highlighted aspects such as patient safety, consent and ethics as important. Many also stated that these should be aligned with ICH GCP and international standards (as summarised above).

The key GCP areas responses repeatedly raised as important are summarised below.

- Ensuring participant rights and well-being are maintained
- Ensuring that participants give full informed consent
- Ensuring all aspects to protect participant safety are retained
- Electronic systems used in trials should comply with GCP
- Ensuring participant data privacy and security of computer systems
- Transparency of data/trial results to the public
- Including patient representation in trial design.
- Ensuring no conflicts of interest in relation to the conduct of trials and pharmaceutical industry
- Ensuring trial documents/data are retained long term and reducing content of records
- Ensuring free treatment for trial participants.

There was support to make the following principles more proportionate:

- Ensuring the training, qualification and experience expected of those involved in conducting a trial is proportionate to the tasks performed. In particular, comments raised

situations where the person was undertaking their normal clinical duties and what the requirements would be for GCP and protocol training, the frequency of GCP training and the documentation required to be obtained/filed.

- Enabling individuals involved in conducting clinical trials to undertake duties they perform in normal clinical practice, e.g., for professions other than doctors or dentists to prescribe medicines, which is currently prohibited in CT legislation.
- Desire for greater flexibility on the information that needs to be recorded and stored, to support the conduct of the trial for example for less documentation to be maintained in both the trial master file and investigator site file, perhaps with further guidance in this area.
- Ensuring proportionate interpretation of the processes and procedures that are necessary to secure the quality of every aspect of a trial.
- Ensuring that participant informed consent is adaptable to cover cluster trials and trials in emergency medicine or where participant lacked capacity to give informed consent.

Government response

Overall, the feedback on GCP principles indicates support for greater proportionality, with some principles identified as particularly important for this forward. It was clear that alignment with international standards, and specifically ICH GCP, is important.

As highlighted above, we will directly refer to the principles of ICH GCP in the legislation.

ICH GCP is currently being revised to build additional proportionality and risk-based approaches into the principles and guidance through an expert panel of Clinical Trial and GCP professionals, in consultation with stakeholders. The MHRA is closely involved in this reform work, contributing extensively to the drafting and review of the revised text.

The revised ICH GCP principles and supporting UK guidance, combined with an overarching expectation in the UK legislation for sponsors to consider proportionate approaches will help empower researchers to utilise risk-proportionate approaches in their trials.

3.8 Sanctions and Corrective Measures

The consultation put forward proposals for additional proportionate sanctions and corrective measures to support regulatory oversight of clinical trials. We proposed enabling regulators to be able to consider information about a sponsor's prior or ongoing serious non-compliance issues in the assessment of an application for a new trial. We also proposed to make it clear that regulatory action can be taken against a specific part of a trial rather than always requiring the whole trial to be stopped, to reflect more modern types of trials.

Question 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?

There were 956 responses of which

- 867 (90.7%) agreed
- 56 (5.9%) disagreed
- 33(3.4%) had no opinion

The majority of respondents agreed with that regulators should be permitted to take into account previous information of non-compliance when considering a new clinical trial application, with some expressing surprise this was not already in legislation. However, several significant concerns were raised with the proposal. Many respondents considered that the regulator already has sufficient power for the most serious systemic cases of non-compliance within individual organisations, such as the ability to stop individual Clinical Trial Authorisations, and through inspection of clinical trial sites, and prosecution. There was a concern that to broaden this further would increase bureaucracy, and drive and reinforce a risk averse culture amongst sponsors. It was suggested any other ongoing clinical trials by the sponsor should be assisted to progress to conclusion under direct oversight by the sponsor and the MHRA.

Questions were raised on how this power would be used in case of suspected on-going serious non-compliance in another country, which may have been discovered by or reported to another regulator.

Some comments supported this power if it was applied to persistent non-compliance with the registration and reporting requirements proposed in the consultation, but there were concerns that the narrowly drawn scope of the corrective measure may prevent this if only applied to "serious and on-going non-compliance". This might mean the UK would be out of step with both the USA and the EU which have legislated to penalise non-compliance with their rules on registration and reporting.

Many respondents encouraged the MHRA to provide a list of examples of "serious and ongoing non-compliance" to reassure sponsors about when these powers might be used. Comments were also received that the applicant/sponsor must be able to appeal the decision, as information on which the refusal was made could be unrelated to clinical trial conduct or be out of date.

Feedback was received that sanctions should be used rarely, reserved for significant infringements, and clear guidance should be given on what infringements would result in sanctions. However, as sponsor organisations may be large organisations running many trials, non-compliance issues for a single trial may not reflect the sponsor's overall ability to conduct trials to appropriate standards and so sanctions should not necessarily inhibit all new trials an organisation intends to initiate.

Government response

Whilst a majority of respondents agreed with the proposal, many respondents brought to our attention the possibility of important unintended consequences that might arise if a new power was written into legislation and therefore, we will not take forward this proposal. Responses highlighted the potential reduction of trials being conducted in the UK and that the measure

would increase reluctance to adopt proportionate approaches. This would undermine the intent of this review of clinical trial regulations for a measure that we would expect to be used very rarely. Given that moving forward, the ethics and regulatory review will be conducted in parallel with close exchange of relevant information between regulators while the review is underway , we consider that there are sufficient mechanisms and powers for ensuring patient safety and data integrity under the current legislation, including reviews of the suitability of the investigator (and supporting staff) and suitability of the site, along with the ability of the regulators to set out any grounds for not accepting an application for an authorisation during their review. Following authorisation, powers already exist for the regulators to require a trial to be amended, suspended or terminated if necessary.

However, non-compliance with new transparency requirements for trials (registration and reporting, as outlined in earlier sections of this document) will be specifically mentioned in the legislation, as constituting grounds for non-acceptance of a request for authorisation.

Question 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?

There were 956 responses of which

- 724 (75.7%) agreed
- 173 (18.1%) disagreed
- 59(6.2%) had no opinion

Respondents largely welcomed this proposal, recognising that it would be inappropriate for a whole multi-arm trial to be halted because of specific concerns about a single arm. Enabling action to be taking against a specific part of a trial will enable such trials to stay open, ultimately benefitting participating patients who may otherwise unnecessarily have treatment interrupted or miss out on the opportunity to take part. However, it was stated that care needed to be taken to evaluate if a problem with one part of a trial reflected a systematic issue with the whole study.

The proposal was seen as risk-proportionate and of particular value for new and innovate trial designs. The advanced therapy community welcomed the proposal. It is very common for advanced therapy medicinal product (ATMP) clinical trials to follow novel designs, and often these studies involve different stakeholders and vendors at different stages. Allowing suspension or termination of a specific part of a clinical trial precludes the impact of the rest of the patient population when the study design allows this. This was considered particularly important when the ATMP is manufactured in small quantities/ is personalised and the targeted disease is rare (i.e., small patient numbers).

Some respondents felt that it was essential to enable regulatory actions to be taken against both a specific part of a trial and/or the trial as a whole.

Government response

The proposal to enable regulatory action to be taken against a specific part of a trial where appropriate, rather than only be taken against the trial as a whole, will be taken forward into the legislation.

Existing powers on the ability of the regulator to amend, suspend or terminate a trial will remain in place. It is the intention of the legislation to enable regulatory action to be taken against both a specific part of a trial and/or the trial as a whole.

3.9 Manufacturing and Assembly

The consultation proposed updates to the requirements for the manufacture and import of investigational medicinal products (IMPs), and their labelling. We proposed to introduce a definition of 'non-investigational medicinal products' (NIMPs – which are often used in support of a clinical trial but are not the actual subject medicine of the trial) into legislation which would allow us to extend the concept to non-medicinal products that may currently be unregulated (such as non-medicinal 'challenge agents').

We proposed to provide greater flexibility in the requirements for labelling clinical trial medicines, for example by enabling a licensed medicinal product that is the subject of the trial to have no, or reduced, specific clinical trial labelling.

We also proposed to extend the current exemption for holding of a manufacturing authorisation specifically for investigational medicinal products (MIA(IMP)) to include diagnostic radiopharmaceuticals within a clinical trial. These products would still need to comply with an appropriate level of GMP, for example under the provisions of a manufacturers Specials licence (MS).

Question 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?

There were 812 responses of which

- 526 (64.8%) agreed
- 176 (21.7%) disagreed
- 110(13.5%) had no opinion

The majority of respondents agreed that we should introduce the term "Non-Investigational Medicinal Product" (NIMP) into legislation. Amongst those supporting the proposal there was a desire for clear guidance to be published regarding the definitions of Non-Investigational Medicinal Products (or Auxiliary Medicinal Products (AxMPs)). If the term 'Non-Investigational Medicinal Products' was to be used, there was a general desire for this to be as aligned as possible with the definition of AxMPs in the EU Clinical Trial Regulations.

There were several comments regarding what would be helpful to include in guidance, in particular, when a NIMP dossier is or is not required, the minimum contents of the dossier, and examples of types of NIMPS.

There was some confusion regarding the use of “medicinal” in the term “non-investigational medicinal products” so there were some proposals to change the term to remove the word ‘medicinal’. There were also several comments with respect to diagnostic radiopharmaceuticals and whether these should be considered as NIMPs or IMPs.
Some responses did express concern regarding the level of licensing and oversight that may be required for certain non-medicinal products such as challenge agents which may increase regulatory burden.

Government response

Non-Investigational Medicinal Products (NIMPs) are currently defined in UK guidance and are not a new concept. Overall, the responses demonstrated support to introduce this term into legislation, similar to the EU Clinical Trial Regulation which has brought the term ‘auxiliary medicinal product’, into legislation rather than in guidance, and we will therefore take this proposal forward. It was clear that appropriate guidance on the manufacturing requirements and regulatory oversight of these will be required, and we will publish detailed guidance to accompany the new legislation.

Whilst there were some comments regarding the word ‘medicinal’ being confusing in the context of NIMPs, the term ‘NIMP’ is well established, and it refers to those materials that are used in support of a trial but that are not an IMP (i.e. not the subject or a reference product within the clinical trial). As such we will retain the terms ‘IMP’ and ‘Non-IMP’ (‘NIMP’) and will include this clarification in the detailed guidance.

Question 32: Do you agree that where a medicine is labelled according to its marketing authorisation (and no blinding is required) that specific clinical trial labelling may not be required?

There were 812 responses of which

- 420 (51.7%) agreed
- 279 (34.4%) disagreed
- 113 (13.9%) had no opinion

The proposal to enable medicines to be used with their marketing authorisation labelling, rather than specific clinical trial labelling did receive a more mixed response, however the majority of responders agreed. It was considered that the proposal would enable greater flexibility, especially where medication was not to be taken away by the trial participant and reduce burden to produce a specific clinical trials label that may contain the same/very similar information to the marketed packaging where this would only be seen by the trial team prior to administration to the patient. The comments received indicated that there was a desire for clear supporting guidance on when specific clinical trial labelling may not be required. For

those that agreed, it was often reiterated that this should be only where the product is used in line with its Marketing Authorisation.

Some concerns were raised regarding not applying a specific Clinical Trials label to supplies taken home by trial participants and suggested that particularly in this scenario there should still be a requirement for labelling, but perhaps with reduced content e.g., trial name, investigator details and directions to aid participant compliance as well as to identify to emergency care practitioners of a patient's involvement in a clinical trial.

Some questions were raised regarding documentation associated with stock accountability, i.e., to capture which trial participant was provided with which medication and when, and whether there would be additional flexibilities for this aspect if clinical trial labels were excluded in some cases.

Government response

The responses generally supported this proposal where it could be justified and subject to the publication of detailed guidance to provide details and examples of when reduced or no clinical trial-specific labelling may be acceptable. We will therefore enable in legislation a risk-proportionate approach to the labelling of clinical trial medicines, such as removing the requirement for a specific clinical trial label where an authorised product in its marketed packaging can be used. This will reduce the production of duplicative labelling. All information already on the licensed packaging will still be required in all cases.

Flexibility in use of clinical trial specific packaging will only be allowed when sufficiently justified and agreed with regulators. For example, it is unlikely that unlabelled medication would be permitted to be given to trial participants to take away, as this would not comply with the labelling requirement for medication in general practice. However, it could be considered where medication was to be given/administered to a patient as a single dose by a health care professional associated with the trial, for example.

The documentation associated with stock accountability will need to depend on the design of the specific clinical trial and demonstration of whether a trial participant had been given trial specific medication was considered important to the trial objectives and endpoints. We will provide guidance on accountability and documentation to ensure clarity on the requirements in different cases.

Question 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?

There were 811 responses of which

- 268 (33%) agreed
- 309 (38.1%) disagreed
- 234 (28.9%) had no opinion

The proposal to exempt radiopharmaceuticals from the need to hold a specific IMP manufacturers authorisation received mixed responses. Of the responses which also provided more detailed written comments, the majority included supportive comments on the basis that another GMP license, such as a Manufacturer's Specials (MS) license was held, such that inspections for compliance with good manufacturing practices would still continue. Where responders agreed with the exemption there was a strong sentiment that this should include radiodiagnostics but not radiotherapeutics (e.g. where radio pharmaceuticals are used to treat a patient), where an MIA(IMP) should continue to be required.

There was clear desire for detailed guidance on what may be included or excluded from the exemption.

Government response

Although more responses to the yes/no question disagreed with the proposal, we have also reviewed the written comments received. The majority of those who provided written comments on the overall proposal agreed but expressed that whilst exempt from holding an MIA(IMP), a GMP licence such as a Manufacturer's 'Specials' licence should still be held. This is in line with the proposal originally described in the consultation. We therefore will proceed with enabling radiopharmaceuticals used as diagnostic IMPs to be exempt from an MIA(IMP).

We are clear that manufacturers will need to hold a valid manufacturing licence and comply with Good Manufacturing Practice, to continue to assure the safety and quality of those products.

The comments received supported the exemption for radiodiagnostics but not for radiotherapeutics. The exemption will only cover radiodiagnostics, we do not intend to extend the exemption to radiotherapeutics. Radiopharmaceuticals can only be administered for processes within hospitals and health clinics. Radiolabelling of patients' blood cells is currently performed within hospitals for routine diagnostic procedures and is not performed under a MHRA manufacturing licence. Radiodiagnostics are routinely manufactured under a Manufacturer's 'Specials' licence and are already safely used in hospitals and health clinics for routine diagnostic procedures.

3.10 Definitions and other Terminologies

The consultation put forward proposals to update a number of definitions in the legislation to modernise UK terminology and promote international harmonisation of definitions, and to introduce into legislation risk-proportionate definitions, which are already set out in UK guidance. For example, changes to definitions we proposed included the following.

Update to definitions of 'clinical trial', 'clinical study', 'low intervention trial', and 'non-interventional trial' to promote international harmonisation. It was, however, proposed to maintain the UK definition of a 'substantial amendment' as stakeholders considered 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.

Simplify the current legislation 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.

We also asked specific questions on proposals regarding investigators, consent and non-interventional trials. The aim of these proposals was to facilitate a more risk proportionate approach to the conduct of trials in the UK without compromising participant safety.

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

There were 397 written responses received, with half of all responders simply stating that they had no comments or concerns on the proposals, with no further detail provided. Around 40% of responders provided detailed comments and a small minority considered no changes were needed to the current UK terminologies at all. Those who provided comments were generally supportive of the proposals.

There was widespread agreement from both organisations and individuals that changing the terminology of “subject” to “participant” was a positive step forward. Some responders did question why this was necessary, and others asked for clarity about whether the term participant would be required to apply across all trial documentation, for example including product labelling.

There were also a number of respondents who advocated close alignment of the definitions used in the UK legislation with the EU, beyond those proposed in the consultation. Conversely other considered that the definition of ‘low intervention’ should be broader than that in EU/OECD.

There were mixed responses to the proposal to maintain the current UK definition of ‘substantial amendment’ rather than aligning with the EU definition of ‘substantial modification’, with some considering that alignment would help facilitate multinational studies. There were also requests to define non-substantial amendments in legislation.

Those who specifically commented on the proposal to facilitate long term follow-up of trial participants after the trial intervention being studied had finished, were strongly supportive of this, commenting that the current framework acts an impediment to this.

There were also several further requests to make the terminology and definitions clearer, these included for the following:

- ‘Principal Investigator’ and ‘study team’
- ‘Interventional’
- ‘Appropriately trained’

- Non-compliance – ‘breach’, ‘violation ‘
- ‘Start’ and ‘end’ of study/trial
- ‘Consent’
- ‘Approved’ – differentiating MHRA and REC and other approvals
- ‘Site’ – particularly in the context of decentralised trials

There were multiple useful comments concerning the proposal to remove the requirement for use of the EudraCT number and replacing with a UK reference number, specifically the Integrated Research Application System (IRAS) Number. While some welcomed this, there were also concerns regarding multi-country trials where EudraCT (or future EU reference numbers) may be used, as well as management of legacy trials that used EudraCT as a reference in the UK.

Government response

There was strong support for updating and modernising the definitions in current UK legislation and we will take the majority of these proposals forward. Having carefully considered the feedback on the proposal not to change the current UK definition of ‘substantial amendment’, we are inclined to agree with comments that the benefits of international alignment outweigh our initial view that the current UK definition provides better clarity. We will therefore introduce the definition of a ‘substantial modification’ into legislation, aligned with the EU definition. Guidance will be developed with stakeholders on examples of what constitutes a substantial or non-substantial modification (we will not introduce a definition of non-substantial modification into legislation).

We will implement the proposal to remove the current legislative requirement for a EudraCT number and instead the IRAS number will be used as a UK reference number. This will have benefits across the research ecosystem as this number will be used by MHRA, HRA and NIHR. International numbers such as the ClinicalTrials.gov Identifier (NCT Number) or numbers assigned in other registries are captured by MHRA systems via the trial application form today and this facility will remain for the EU reference number in future, however, the UK reference number will be that used officially.

To answer concerns on the change from ‘subject’ to ‘participant’, we can clarify that this proposal is to replace the term in the UK legislation itself and will not impact the terminology allowed to be used by a sponsor in multi-national trial documentation.

We will work with the research community, particularly those running cancer trials and/or advanced therapy trials to develop guidance to accompany the new measures to facilitate long term follow-up of trial participants after the trial intervention being studied had finished.

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

848 written responses received

There was overall support to expand the professional groups who can be an Investigator. A risk proportionate approach was very much supported, where who can be an Investigator should be proportionate to the trial design and the type of medicine under study, for example a phase 1 trial investigator should be a physician whereas later phase trials or for proportionally lower risk trials it may be possible to allow for a wider number of roles as the Investigator. Responses also highlighted that the role of Investigator should be clearly defined, ensuring the necessary training is in place, and that they have appropriate qualifications and experience in the field under investigation. Responses also highlighted the need to future-proof the proposals, a recent example being consideration for decentralised trials where there may not be a traditional type of investigator. Additional roles that could act as investigators was suggested as being possible in guidance, so they can be reviewed as needed.

There were a wide range of suggestions about specifically who should be able to act as an Investigator. The majority of responses stated that the investigator should be an expert health care professional. Whilst many supported that the investigator should be an expert, there were also a significant number of responses to support the notion that the investigator does not necessarily need to be a medical doctor if they are qualified in a relevant field. Some considered only recognised professions should be Investigators, for example those affiliated with a specific royal college. Some responders suggested anyone who would usually care for that patient could be an investigator – this would widen up the role of investigator to professions such as pharmacists and psychologists, and would also include midwives, who often have prescribing as part of their usual practice. Healthcare professionals that belong to a professional regulatory body and that are appropriately trained and expert in their field should be able to act as Investigator in a trial.

Government response

We will take forward these proposals, with an aim to keep the legislation future-proof and using guidance to provide clarity on the detail of professional roles that are suitable, so that the listings can be updated as professional practice changes. We will co-create this guidance with the research community and patients.

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

There were 947 responses of which

- 698 (73.7%) agreed
- 165 (17.4%) disagreed
- 84 (8.9%) had no opinion

There was a significant majority, who supported the proposal. Responders particularly noted that “appropriately trained and qualified” needs to be very clearly defined so that there is no misunderstanding. Even if someone seems to have appropriate training and qualifications there may still be specific elements of a trial that require additional training, and this should be made clear in guidance. There should also be consideration for who is responsible for providing the relevant training.

The responses highlighted a clear desire to take a risk-proportionate approach to who can seek consent, and for that approach to be clearly detailed and communicated in guidance. Several comments stated that trial sites often have specific requirements for who can seek consent that can hamper research especially for lower risk trials, so considerations for a risk-proportionate approach would assist in those scenarios. Many responses suggested that a member of the investigators team should be able to seek consent if they are appropriately trained, highlighting that in many cases there will be members of the investigators team that are highly qualified to talk – and listen – to participants, a cited example being midwives.

Some responses were concerned about consent indemnity, expressing uncertainty around whether it is the chief investigator who is responsible for the consent process.

Government response

We will take forward these proposals, using guidance to provide clarity on the considerations for determining the suitability of the professional roles, qualifications and training under different circumstances, so that risk-proportionate approaches are taken at both the local level and study level.

Question 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?

There were 947 responses of which

- 487 (51.4%) agreed
- 234 (24.7%) disagreed
- 226 (23.9%) had no opinion

Many of the responses to this question concerned the more general proposal for long term follow-up (LTFU) (allowing 'non-interventional' long term follow up information to be collected after intervention end without the need for regulatory approval), as well as the specific question posed on use of the non-interventional follow-up for real world data (RWD) collection as part of "approved" use. Overall, the plans for both non-interventional LTFU and collection of RWD were strongly welcomed. In particular there are certain indications, such as oncology, or for certain medicines, such as advanced therapies, where follow-up may go on for many years, and allowing much of that to be conducted in a non-interventional study was welcomed. A few comments asked for clear guidance on what was meant by non-interventional.

Many of these responses were concerned that the LTFU could impact data privacy and that there would be wider data protection considerations such as the UK General Data Protection Regulation (UK GDPR) considerations that need further consultation. Responses also highlighted that any proposal for LTFU should be clearly stated in the initial interventional trial proposal to aid confidence that the LTFU can be conducted outside the Clinical Trials legislation as appropriate. It was also frequently mentioned that guidance on different LTFU scenarios would be helpful, with some examples or case studies, as well as what approvals would be required.

Government response

We are not taking forward this proposal, because recent legislation to provide a legal basis for the Early Access to Medicines Scheme (EAMS) has made changes to facilitate the collection of real-world data. We consider those changes will support the appropriate collection of data on the use of an unlicensed medicine, and further legislative amendments are not required at this time. The Early Access to Medicines Scheme is one of the key regulatory routes that gives patients access to a medicine before it receives a licensing authorisation, where there is an unmet medical need. The legislative changes for EAMS made it clear that collection of real-world data on the use of a medicine in the clinical setting used during the EAMS scheme does not require a Clinical Trial Authorisation but can be collected dependent on an MHRA EAMS Scientific Opinion approval and subject to patients' informed consent. This is an important step forward in supporting the gathering of evidence about the medicine during clinical practice, but outside of formal clinical trials.

Comments about the collection of long-term follow-up information after the trial intervention being studied had finished have been addressed in consideration of the question about definitions above.

3.11 Conclusion section

The final section of the consultation sought feedback on the proposed changes overall and gave opportunity for respondents to provide information on any additional aspects of the clinical trials legislation they would like to be considered.

Question 38: Do you agree that the proposed changes introduce improvements to streamline processes and to remove unnecessary burdens to trial sponsors?
There were 2138 responses of which

- 1213 (56.7%) agreed
- 318 (14.9%) disagreed
- 607(28.4%) had no opinion

There was widespread support for streamlining and adding additional flexibility and agility into the legislation, with many responders commenting that the proposals would make the UK a more attractive place for clinical trials to be conducted. It was considered to make the legislation more future looking and support flexibility in new approaches to trials. Over-legislation and over-interpretation of legislation was a concern, with some responders considering it key that putting too much in legislation could lead to additional unnecessary and undermine the aim of streamlining.

Responders also highlighted that a certain level of burden is good as that burden serves to ensure standards of patient safety. Some expressed concern that streamlining processes for clinical trials must not be at the expense of the safety of those participating in clinical trials, and that streamlining might cause some patient safety issues.

A minority of responders said the current legislation was already sufficient, or the proposals outlined in the consultation were too legislation heavy. Responders noted the importance of clear and robust guidance, to provide sufficient detail and to support clear interpretation of any new legislation.

Government response

The majority of responders expressed support for the overall set of proposals and considered that they would be beneficial to clinical trials in the UK. We will be proceeding with the proposals as outlined in the individual responses to each question above. We have heard the concerns that have been raised, particularly regarding patient safety. Patient safety is of paramount importance and trials must be conducted to the appropriate standards to assure the safety of those who participate in trials. The measures proposed to streamline application processes are intended to facilitate good, safe research while ensuring appropriate regulatory scrutiny of trials. The proposals address some of the requirements in our current legislation that are duplicative or do not provide additional value in identifying or addressing safety risks.

Question 39: Are there other aspects of the Clinical Trials legislation that you believe have not been considered? For example, is there something you think we should prioritise for consideration in the second phase of legislative changes.

A key aspect that responders highlighted needed further consideration was ensuring alignment with the EU clinical trials process (and also the USA in some cases), with many responders expressing that they would like as close an alignment to EU legislation as possible, so that duplication of work is minimised. It was also noted that in the case of trials involving genetically modified organisms, alignment with other UK departments such as Health & Safety Executive and Department for Environment, Food and Rural Affairs is needed.

There was a request for a legislative requirement for guidance to be co-produced by regulators with stakeholders, to ensure that those with relevant experience and expertise are involved in the development of the guidance.

Transparency of results and publication of data were also frequently mentioned, with many responders desiring that the results of all clinical trials, and resulting data, must be published in all cases, including those trials that halt early.

Concerns about staff training were also raised, in particular from with organisations expressing worry over the resource needed to retrain staff in order to comply with potential new legislation requirements in areas such as diversity.

Government response

We have heard the concerns around ensuring alignment with other international processes, and those concerns are addressed in the individual sections above where they arise. We are

clear that international standards for clinical trials will be maintained, and whilst legislative changes may streamline how clinical trials are approved in the UK, the core documentation and evidence to support a clinical trial application will remain aligned with international expectations.

We will be introducing new transparency measures to ensure greater transparency of results, including ensuring trial results are made available. The transparency section of this document above deals more explicitly with our proposals to increase transparency.

We recognise concerns about resourcing and training needed to comply with new requirements, and we will ensure there is comprehensive guidance to support clear understanding and interpretation of the new regulations. We are taking forward a range of changes intended to reduce administrative burdens, streamline process and make it easier to carry out trials in the UK, helping to support investigators to focus their resources on running the best possible clinical trials.

We are committed to preparing the accompanying guidance in partnership with patients and stakeholders across the sector to ensure that we get it right, and those who are involved in the day to day running of trials share their knowledge and experience. There will be further opportunities for partners to work with us in the drafting of these documents.

Question 40: 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?

There were 2135 responses of which

- 697 (32.6%) agreed
- 167 (7.8%) disagreed
- 1271 (59.5%) had no opinion

The majority of responders expressed no opinion. Of those who provided further detail in their response many raised geographical inclusion, highlighting that it was difficult for those in rural areas to partake in trials. Most comments regarding the impact on those who live in NI expressed the need for the outcome of discussions around EU Exit impacts to be completed.

Whilst not a protected characteristic, it was frequently mentioned that trials have a large literacy requirement which makes it difficult to understand and makes informed consent more difficult as the participant may not always understand the documentation.

Government response

A number of the changes we intend to take forward will support greater public involvement in trials and help widen accessibility of trials to benefit more patients across whole of the UK. The new requirement to work with people and communities in the development of a trial will

mean participant voices are included in the way trials are designed and conducted. We will also simplify the way patients consent to participate in cluster trials using already-approved medicines. Introducing lower-burden consent requirements means that patients will still receive critical information to consider participation but are supported to give their consent in an easier way. Encouraging researchers to take a more proportionate approach to seeking consent will help avoid participants receiving long and detailed information that can be difficult to understand.

Question 41: 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? If so, please provide details.

There were 2135 responses of which

- 239 (11.2%) agreed
- 500 (23.4%) disagreed
- 1396 (65.4%) had no opinion

The majority of responders expressed no opinion. Of those who provided more detailed comments, most mentioned the need to tread carefully where trials concern pregnant women and children, with some respondents suggesting that pregnant women should not be included in trials.

Similar to the above question, responders also mentioned the issue of those living and working rurally being excluded from participating in trials.

There were also several responses indicating that trial participation needs to focus on the target population of the medicine being trialled.

Government response

Lack of diversity can be an obstacle to understanding the safety and efficacy of novel therapies across subgroups of the population. It is critical that clinical trials fully represent the population affected by the specific disease under trial. This is particularly important for those often under served by research, such as pregnant individuals and children, and that all groups have the option to access safe clinical trials for appropriate medicines and can trust that licensed medicines prescribed to them are supported with relevant evidence. As described above, we are taking forward a number of changes that will support greater diversity in clinical trials and more patient and public involvement in the set up and design of trials.

We are also taking forward a number of changes to make the UK regulatory environment more attractive for sponsors to bring their trials to the UK, this will support more trials to be run on all kinds of medicines, which will help patient access to more trials across the whole of the UK.

Question 42: Do you have any evidence that we should consider in the development of an equality assessment?

The vast majority of responders did not provide evidence for us to consider. However, several responders sent links to articles, papers and studies regarding equality assessments. Other points that were raised included the difficulty of ensuring equality in specific trials such as in rare diseases, ensuring that trials need to be shaped by the setting in which they take place, ensuring that the people for whom a medicine is designed are included in the trial, and ensuring that literacy levels are taken into account.

Government Response

We will consider the detail of the evidence shared to support the completion of an equality impact assessment for the new legislation. The changes we will take forward following this consultation are intended to make it easier to run trials and make the running of those trials more efficient. This will ultimately support more trials, for more kinds of medicines coming to the UK, and bring the benefits of innovative medicines throughout the UK. By ensuring the UK environment remains attractive for multi-country trials we will facilitate rare disease research where the incidence of the condition is low and requires recruitment from multiple countries.

4. Section 2 of the Medicines and Medical Devices Act

The consultation was carried out in accordance with the requirement in Section 45 of the Medicines and Medical Devices Act 2021.

For medicines, the appropriate authority is the Secretary of State in relation to Great Britain and the Department of Health in Northern Ireland in relation to Northern Ireland.

In making regulations under section 2 of the Act, the overarching objective is to safeguard public health.

In considering this policy, and regulations that would be needed to give effect to it, the appropriate authorities have had due regard to:

- the safety of medicines within the scope of this policy
- the availability of medicines within the scope of this policy
- whether the United Kingdom is likely to be seen as a favourable place in which to: research the medicines within the scope of this policy, develop medicines within the scope of this policy or manufacture or supply medicines that come within the scope of this policy

We have assessed the clinical trials proposals against these factors, as described in the consultation document, and evidence submitted in the consultation responses has not changed those assessments.

The Clinical Trials proposals intend to strengthen how we safeguard public health and ensure patient safety is prioritised by:

- Increasing transparency of clinical trials that are being conduct through new statutory requirements to register clinical trials, to publish a summary of results, and trial findings with participants.
- Making trials more patient centred with new guidance to support trials to involve people with relevant experience, such as a patient, family member or carer, in the design and conduct of a trial and, support greater diversity in clinical trial populations, ensuring there is alignment with established international standards that ensure all trials are run appropriately to protect the of trial participants.
- Extending the requirement to follow good clinical practice to service providers of electronic systems that may impact on patient safety.
- Allowing regulatory action to be taken against specific aspects of trials.

Collectively, these proposals will make it much easier to run clinical trials in the UK. This will support more sponsors to trial new medicines in the UK, and therefore increase the development of new innovative medicines that will benefit patients.

The Clinical Trial proposals also intend to make the UK a more favourable place to develop medicines by providing a more flexible and enabling regulatory regime to support greater innovations in clinical trials and be more adaptable to different types of trials. This includes:

- embedding the successful MHRA/research ethics committee combined review into legislation with competitive timelines for review of applications
- streamlining reporting requirements and removing duplication wherever possible, whilst maintaining our oversight of participant safety
- introducing a “notification scheme” for trials where the risk is similar to that of standard medical care, enabling the clinical trial to be approved without the need for a regulatory review and conducted in a risk-proportionate manner
- Amending Request for Information (RFI) receipt so that the sponsor has access to RFIs as they are ready rather than waiting for all requests to be made together
- Adding more elements of risk proportionality to the trials process, and including risk proportionality in the GCP
- Introduction of more streamlined, efficient, and competitive approvals for trials, whilst maintaining international standards for trial conduct, to support the UK as a site in multi-national trials.

Throughout this Government response, the MHRA hopes to have demonstrated how we have listened and responded to themes concerning patient safety, safeguarding of public health, and the favourability of the UK as a place to conduct clinical trials.

5. Conclusion and next steps

We welcome the great engagement with the consultation and appreciate the constructive and considered responses received and the vast range of support, suggestions and concerns that were raised throughout. Having carefully considered all responses, we will now take forward new legislation to update, improve and strengthen the UK clinical trials legislation, as outlined in this response document.

We will work with lawyers to begin drafting new legislation to introduce these changes to the regulation of clinical trials. As we draft the legislation a key focus will be ensuring flexibility but making sure the legislation still provides the necessary legally enforceable requirements so that we can assure the safety of trial participants and the quality of trials.

We know that pragmatic and consistent interpretation of the new legislation will be key to successful implementation. We will be preparing comprehensive guidance to accompany the legislation. Many responses provided helpful input highlighting issues that this guidance should cover. We will work with partners and stakeholders nationwide to co-create the accompanying guidance, to ensure that it benefits from those with valuable knowledge and experience of running and participating in clinical trials.

Importantly, these legislative changes support a wider coordinated programme of work that has been developed to ensure the Recovery, Resilience and Growth (RRG) of UK clinical research, as set out in the Government's bold vision for the future of clinical research delivery. Through this vision and plan, the research ecosystem across the UK is working together to achieve our aim of making the UK world-leading in efficient and cutting-edge clinical research.

We thank everyone who took the time to respond to this consultation and for helping us shape the future regulation of clinical trials.