

The Academy of Medical Sciences promotes advances in biomedical and health research and supports efforts to translate these advances into healthcare benefits for society. In February 2022, the Medicines and Healthcare products Regulatory Agency (MHRA) consulted on a set of proposals to improve and strengthen the UK clinical trials legislation to help us make the UK the best place to research and develop safe and innovative medicines. Our response is based on our previous policy relevant to clinical trials legislation, patient and public involvement and diversity, as well as written evidence from members of our elected Fellowship, which includes some of the UK's foremost experts in the NHS, academia, and industry. The consultation asked for evidence on 43 questions.¹

Note: this response will be submitted via the consultation's online portal.

Consultation questions

Patient and public involvement

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

Yes.

Although we have selected 'Yes', there are important caveats to this opinion, described below.

The Academy strongly agrees that the involvement of people with relevant lived experience (PPI) is highly valuable in the design, management, conduct and dissemination of clinical trials and we encourage the introduction of legislative duties that can drive a cultural change in clinical research to one that truly values the contributions of patients. However, we have heard strong concerns that including a legislative requirement for PPI at every stage of a clinical trial could increase the administrative burden on both sponsors and patient contributors without proportionate benefit. Therefore, taking all evidence into consideration, we emphasise the importance of allowing justification of where PPI is not possible or appropriate in the application process, as suggested in the proposal, enabling a case-by-case assessment of clinical trials. More detail and best practice examples should be shared in accompanying guidance, developed in consultation with relevant stakeholder groups, to help avoid a tokenistic approach to PPI.

The value of patient and public involvement in clinical trials

The Academy and the Fellows consulted strongly agree that the input of people with relevant lived experience – patient and public involvement (PPI) – is highly valuable in the design of clinical research trials. Relevant lived experience results in better studies that

¹ Medicines and Healthcare products Regulatory Agency (2022). *Consultation on proposals for legislative changes for clinical trials*. <https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials> [accessed Wednesday 9 February 2022]

seek to answer the questions that are important to patients and is appreciated by sponsors, including commercial organisations as well. Meaningful PPI can reduce unnecessary or overly burdensome procedures, improve patient recruitment,² retention, and experience, and reduce cost. It can provide invaluable insight into the acceptability of a protocol, the relevance of outcome measures, the accessibility of patient-facing materials (including consent forms and dissemination of trial findings), and the interest and support that can be expected for a given trial. Patient involvement can also provide insight into how to achieve broad representation of affected populations in clinical trials. To best achieve this, involvement should include those in the target patient population who will have most difficulty with access and whose need is greatest.³

Given the high value of PPI to clinical trials and the burden that involvement can pose to patient and public participants, the Academy supports NIHR guidelines for the reimbursement of patients and members of the public involved in research. Any changes to clinical trial legislation or guidance should recognise this need for reimbursement and the additional economic costs PPI places on those running clinical trials.

We welcome the stated intention in the consultation to co-develop guidance with relevant external experts and stakeholders, including patients and trial participants. However, we noted that this intention was caveated – ‘*unless required on an emergency basis*’. More broadly and based on the Academy’s work on the lack of PPI during the COVID-19 pandemic and in line with the HRA,⁴ we would caution against making exceptions to emergency situations as PPI can be particularly important in these cases to ensure quality of and to retain public trust in scientific results and the regulation of research. During the first wave of COVID-19, there was a decrease of studies involving patients and the public, from 78% in 2019 to 20% in the first 40 trial submissions received during the COVID-19 pandemic.⁵ Suggesting emergency situations are exceptions to the need for PPI risks casting aside PPI when the need may be greatest.⁶ We acknowledge that the system is not currently set up to enable rapid response PPI and support will need to be put in place to make PPI possible in emergency situations.

How to encourage PPI in clinical trials

The Academy and the Fellows that we consulted agree about the value of public involvement and support moves to encourage it in the most meaningful way. It is hoped that the proposal in the consultation document will help to engender deeper cultural change so that research is more patient-centred. However, we welcome the proposal to allow sponsors to justify where PPI was not appropriate or possible; without this, a legal requirement for PPI at every trial stage risks creating unnecessary challenges or delays,

² Ennis L & Wykes T (2013). Impact of patient involvement in mental health research: longitudinal. study Br J Psychiatry 203(5):381-6

³ Academy of Medical Sciences (2021). *People’s Perspective COVID-19: Preparing for the Future*. <https://acmedsci.ac.uk/file-download/57914133>

⁴ Academy of Medical Science (2020). Public involvement and engagement in research during the COVID-19 pandemic workshop. Tuesday 19 May 2020. <https://acmedsci.ac.uk/file-download/77957062>; Health Research Authority (2021). *Public involvement in a pandemic: lessons from the UK COVID-19 public involvement matching service*. <https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/public-involvement-pandemic-lessons-uk-covid-19-public-involvement-matching-service/>

⁵ Hanley B & Tarpey M (2021). *Involving the public in COVID-19 research: a guest blog by Bec Hanley and Maryrose Tarpey*. Health Research Authority, Thursday 30 April 2020. <https://www.hra.nhs.uk/about-us/news-updates/involving-public-covid-19-research-guest-blog-bec-hanley-and-maryrose-tarpey/>

⁶ Academy of Medical Sciences (2021). *People’s Perspective COVID-19: Preparing for the Future*. <https://acmedsci.ac.uk/file-download/57914133>

adding work and economic costs (to both sponsors and patient and public contributors), and resulting in tokenism or a tick-box approach to PPI, without proportionate meaningful benefit. PPI involvement may not always be straightforward; for example, in prevention trials (e.g., of vaccines or anti-hypertensive drugs), both those affected by the condition, and those who are the target of the intervention (but may otherwise be healthy) will have important, but potentially conflicting views. In disease outbreak trials (e.g., COVID-19, Lassa fever) it is also difficult to know who to involve as there may be few (if any) people affected by a disease at the point at which the trial is being designed, and any existing patients may (depending on the condition) being severely acutely ill and unable to participate in PPI activities. In such cases, PPI may only be possible at some stages of a clinical trial, rather than all. It is also worth noting that international trials initially designed outside the UK (e.g., a multinational pharmaceutical company trial of a new drug) may not have fully involved patient perspectives or may already have done so, but outside the UK.

Therefore, the exact nature and contributions of PPI will and should vary from trial to trial. Public involvement is a 'means to an end' – with a goal of improving research and healthcare – and is not an end in itself. The ultimate aim of any legislation must be to ensure clinical research is clearly focused on patient needs and priorities; so, focusing legislative duties very narrowly on mandating PPI in every scenario could be counter-productive, making researchers focus resources on the process rather than the desired outcome.

Research transparency

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

Yes.

Registration is an essential step for any clinical trial, including devices and non-drug trials. The development of trials registries (such as Clinicaltrials.gov, EudraCT and similar) has been incredibly valuable in terms of enabling patients and doctors to find studies to participate in, and to avoid duplication of effort when planning new research projects. Having a requirement in the legislation would not be a burden on the majority and would ensure visibility of the few choosing not to do so. We also heard some support for penalties for non-registration, such as ethics withdrawal if a trial is not registered by the date of first patient recruitment. To avoid duplication and ensure international compatibility, trials should be required to register with registries that already exist, rather than setting up new registries.

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

Yes.

The publication of a publicly accessible summary of trial results in a timely manner is becoming standard outside the UK and should be legislated. It ensures reporting, particularly of studies with negative results, so reduces the risk of patients being asked to participate in a futile study that makes no meaningful contribution to the field. It will be important to be flexible in terms of acceptable formats of the results summary. Requiring one specific format only would result in additional work and a duplication of effort if, for example, the results have been published elsewhere as a paper. We have heard general support for a time limit of 12 months after the end of the trial. However, it will be important

to define what is meant by the 'end of the trial', whether that is the end of the follow-up required to achieve the primary outcome measure, the time to ensure that all requisite data have been received, or similar. This will be a particularly complex question for some adaptive trial designs that do not have a clear point of completion, such as 'living trials' (e.g., case study 3, AMS FORUM report on '*adaptive trials: acceptability, versatility and utility*').⁷ As with many of these proposals, it will be important to develop guidance with additional details and support about what is required from a results summary.

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

Yes.

The requirement to offer to make trial findings available to participants would be a good addition to the legislation and would be welcomed by participants, who often express the desire to know the results of trials they commit time to. Having this requirement in the legislation will mean trial teams have to build this into their routine processes.

While legislation should set out the principle that trial results are made available to participants, the operational details of how this is achieved should be addressed in the guidance. Sending trial findings to patients directly may be challenging. For example, many participants may have ceased to be involved before the end of a trial, before the results are available; some may have died, or moved residence, doctor, or healthcare provider, or lost touch with the investigator; investigators may have moved roles or retired, and investigative sites may have closed. Data privacy issues may make it difficult for sponsors to mail results directly to participants. There are examples of good practice in this area and doubtless more that could be developed. For example, in some trials it has been possible to mail thousands of participants directly from centrally held databases of participant contact details. For others, it has been possible to explain to participants during the consent process or through information provided during the trial where and when the results will be made available (e.g., on a website).

We have also heard that there could be occasions where the data might still be confidential in terms of intellectual property rights. So, whilst a commitment to transparency is not unreasonable, any requirement will need to take into account the fact that there could be occasions where data is still confidential.

Combined regulatory and research ethics approval

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

Yes.

The clinical trial environment is becoming increasingly competitive internationally and it is vital that the UK is not left behind because of delays in the approval process. A combined approach with the proposed clearly defined timelines would reduce administrative burden for the trial sponsors, helping to keep the UK internationally competitive. At an event that we held recently, we have heard positive feedback about the current combined submission

⁷ Case study 3 on page 18. Academy of Medical Sciences (2019). Adaptive trials: acceptability, versatility and utility workshop. Wednesday 23 January 2019. <https://acmedsci.ac.uk/file-download/36842538>

approach used by the HRA.⁸ Provided that the protection of patient safety is not compromised, steps to streamline processes such as these are to be welcomed. Introducing an additional limit on the time taken by the MHRA and HRA to validate submissions could streamline the process further.

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

Yes.

We support the proposed sponsor-driven timeline to respond to any requests for further information as this streamlines processes while retaining flexibility for sponsors to enable international collaboration and increasing accountability.

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

Yes.

A 10-day maximum to reach a combined MHRA and ethics final decision would be a welcome, internationally competitive timeline. However, we have heard that the tight timeline might be a challenge for some ethics committees, who are volunteers, so a light-touch review system may be required.

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

Yes.

If safety considerations require further independent advice, then the addition of up to two months is reasonable. However, this should be the exception not the rule. Guidance should be issued with more details about which kinds of trial might require the regulators to seek independent advice. Such guidance will enable sponsors to account for the additional time in trial planning and enable sponsors to anticipate the need for additional advice and update their application accordingly. It would also be useful for sponsors to be notified at the earliest possible opportunity when the regulator decides that independent advice and a timeframe extension is needed. Without clear guidance and communication, we have heard concerns that this provision could cast doubt on the commitment of the MHRA to the standard timelines proposed earlier in this consultation.

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

Yes. Option 4 - Legislative change allowing for exemptions if a good rationale is provided in the protocol and approved by the competent authorities

We have heard support for legislative change with the time limit set in the guidance that allows for exemptions if a good rationale is provided in the protocol and approved by the competent authorities. Academically sponsored trials can be extremely slow to recruit, as can trials in particular disease areas, such as rare diseases where patient numbers are limited. There should be a clearly stated duty for the investigator to consider halting

⁸ <https://acmedsci.ac.uk/more/events/the-hra-at-ten> [Last accessed Monday 07 March 2022]

recruitment where the management standard of care has moved on and rendered the study question obsolete. The rate of change in standard of care varies enormously between diseases and over time and this should be taken into account. Nevertheless, it is reasonable and certainly simplest to have a time-based criterion for an investigator to confirm that the research question remains valid. The investigator should also justify why a study that has not recruited by the two-year time limit should remain open. We heard general support for the proposed time limit of two years, with those unsure agreeing that two years was a good starting point and, as long as the limit is placed in guidance rather than legislation, the time limit could be more easily modified by MHRA based on experience.

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

Yes.

Guidance would be preferable to legislation to provide flexibility. However, clarity should be provided on what types of documents are essential and what types are optional to ensure critical documents are not missing causing delays, since ethics committees do need a minimum document set to be able to make a decision.

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

Yes.

Giving trial sponsors sight of requests for further information (RFI) when they are ready would seem a very sensible step to help with efficiencies. However, if sponsors get serial minor requests and are required to put them each through internal processes individually, this would be cumbersome and would be regarded by sponsors as uncompetitive. It would also be useful to know which parts of the application have been found satisfactory so that parts of the sponsor team can be reallocated.

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

Yes.

The ability to receive an RFI during the review of a substantial amendment would be useful. It would also be useful if trials halted for non-safety reasons were allowed to restart without another safety approval.

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

Yes.

A notification scheme is a reasonable approach for low- and non- intervention trials provided that full research ethics committee (REC) review is maintained. 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.

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

Yes.

Although there is support for the concept of notification schemes, we have heard concerns that the OECD definition of a 'low-intervention trial' is not broad enough. For example, we have been told that a trial of a well-known and widely used drug such as aspirin for the prevention of cardiovascular events would be considered low risk but the same trial in the

same population that sought to obtain information on the development of colorectal cancer would not. In addition to setting out the principle of a low-intervention trial notification scheme in legislation, the suggestion was made that:

- A legislative mechanism is built in for the MHRA to “re-classify” a full application as “low-intervention” at any point during its journey from submission to approval (and similarly at any subsequent substantial amendment).
- And/or a formal light-touch system is introduced to advise if a study satisfies the definition of low-intervention.

It has also been suggested to us that the long-term follow-up phase on clinical trials could be beneficially re classified as non- or low- interventional. Once the ‘main’ phase of a clinical trial is complete and the primary and other key analyses are available, analysed and reported, many trials have a long-term follow-up phase. Long-term data collection of a randomised controlled trial allows for reliable (unbiased) assessment of the effects of the initial randomised treatment on both safety and efficacy. During this period, no medication is issued as part of the trial (although depending on the circumstances, including the results of the trial and licensing status of the intervention, some or all patients may receive the active study drug as part of routine clinical care). In the context of long-term follow-up, the protocol and associated ethics approval needs to remain open/valid, so it is not appropriate to fully close the trial. However, since there is no ongoing administration of study treatments as part of the trial and participants will be under the usual care of the health services, such trials should be re-categorised as “non-interventional”. Therefore, it was suggested that: a legislative mechanism is built in to allow long-term follow-up of clinical trials (e.g., through linkage to routine healthcare data or periodic patient questionnaires) can be “re-classified” as “low-intervention” or “no-intervention” once the main treatment comparisons have been complete.

The details of each of these suggested changes can then be defined in guidance, to expand on each of these points. Additional guidance should be co-developed by MHRA and people/organisations with relevant experience and expertise (including clinical trialists, clinicians, and patients).

Concerns were also raised that the suggestion that any placebo used in the trial is either a marketed product (e.g., saline) or has been manufactured under an MIA(IMP) with a formulation that matches the marketed product (with the exception of removal of the active substance) seems too restrictive. There are likely other ways to produce placebo (e.g., over-encapsulation) that could pose no additional risk to the participants, and which should be included.

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

Yes.

We heard general support in our consultation with Fellows for the proposed provisions for clinical trial approvals, including a notification scheme for low-intervention trials. However, a significant concern will be sponsor doubt about appropriateness of a particular study for notification, especially as imprecise terms such as ‘extensive’ and ‘sufficient’ are used in the definitions. As discussed in our answer to question 13 B), concerns were also raised that the OECD definition of a ‘low-intervention trial’ is not broad enough. Therefore, in addition to setting out the principle of a low-intervention trial notification scheme in legislation, the suggestion was made that:

- A legislative mechanism is built in for the MHRA to “re-classify” a full application as “low-intervention” at any point during its journey from submission to approval (and similarly at any subsequent substantial amendment).
- And/or a formal light-touch system is introduced to advise if a study satisfies the definition of low-intervention.

As discussed in more detail in our answer to question 13 B), we have also heard 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 “re-classified” as “low-intervention” or “no-intervention” once the main treatment comparisons have been complete.

The details of the proposed provisions and each of these suggested changes should be defined in guidance, to expand on each of these points. Additional guidance should be co-developed by MHRA and people/organisations with relevant experience and expertise (including clinical trialists, clinicians, and patients).

Research Ethics Review

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

The proposals to reduce the restrictive legislative provisions for the make-up and proceedings of research ethics committees (RECs) are appropriate; such details are better placed in guidance and policies. However, these important committees need a mix of lay and expert members, and the chair needs research trials experience. Maintaining a balance of expertise is critical and the input of patients and public is increasingly important. RECs are useful fora to consider whether the study design, its participant/patient information sheet (PIS), and other patient-facing materials are sufficiently accessible and relevant to affected populations.

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

No opinion.

Please provide further details. E.g., if yes, what legislative requirements could be introduced to better support increased diversity in trial populations?

We would welcome measures that support trialists to achieve clinical trial participant populations that reflect the diversity of the target population for the intervention being tested. However, diversity is a complex, heterogeneous concept. Without more detail about what is being proposed, we cannot support introducing legislative requirements to support diversity because there is potential for unintended adverse consequences. For these reasons and because legislation is less easy to modify than guidance, we have heard that improving diversity in clinical trials would be better encouraged through strong recommendations in the guidance and sharing best practice.

Diversity in clinical trials, and particularly achieving a trial population representative of the target population, is an important area to ensure the quality of scientific evidence in real world populations. It was noted that some of the other proposed legislative changes in this consultation and improvements to regulatory guidelines will help improve diversity as well, such as increasing the amount and quality of involvement of relevant clinical and patient groups and developing guidelines that shape and govern clinical trials. We heard some support for a requirement for a diversity assessment/justification showing efforts to include a population representative (including geographically) of the population affected

by the disease being addressed (in-line with guidance from the FDA). Approaches to improving accessibility to and inclusivity of this population could include translating the PIS into languages relevant to the target population or having trial sites that match the geographic distribution of the target population (though this may be unrealistic in certain fields such as rare diseases). However, as discussed below, the complexity of the issue and barriers to diversity in clinical trials may mean that such approaches and requirements are better placed in guidance rather than legislation.

Diversity is a complex, heterogeneous concept with many, often intersecting dimensions relevant to clinical trials, including sex/gender, age (elderly, children, neonates), ethnicity, geography (urban/rural, north/south), socio-economic status, co-morbidity (physical, mental health), co-medication, care setting (hospital, primary care, community, etc). To add to this complexity, the details of how diversity is defined and how it should be addressed are likely to change over time – concepts of gender, sexuality, ethnicity, and various aspects of health have changed substantially over recent years and are likely to evolve further in the future. Any approaches for improving diversity in clinical trials would need to be individually defined with a clear goal and an evidence-based approach, in consultation with the groups in question. The barriers to achieving the diversity in trial participants that matches the target population are complicated and difficult to overcome and a legislative requirement would render many trials impossible to carry out. Because of the complexity of the issue, there is also a risk of unintended adverse consequences of any changes. If enshrined in legislation that is relatively difficult to modify, any unintended adverse consequences might be difficult to rectify. For these reasons, many experts we spoke to suggested that improving diversity in clinical trials would be better encouraged through guidelines and sharing best practice rather than legislation and fixed regulation.

As mentioned in the proposals, one well-recognised challenge is the inclusion of pregnant and/or lactating individuals. The Academy supports the clinical trial and regulatory community in working towards safe inclusion of pregnant women in clinical trials as a default position with justification provided where this may not be appropriate.⁹ It should also be noted that there are gender differences in clinical trial registration with representation of women in earlier stages of the drug development process remaining low (~22% in phase I clinical trials),¹⁰ regardless of pregnancy/lactation. The Academy would support legislative requirements that the gender balance of participants in phase I, II and III clinical trials reflect the gender balance of the target population for the intervention being tested, with justification provided where this may not be appropriate. Furthermore, many clinical studies still fail to power and stratify their results to identify sex-specific side effects or outcomes.¹¹ For example, despite well-known sex differences, women comprised on average only ~27% of participants in the 36 landmark trials for congestive heart failure between 1987 and 2012 and of those only 44% conducted gender-based subgroup analyses.¹² The Academy recommends that the MHRA requires that gender be routinely considered as experimental variables in clinical research designs, analyses, and reporting, with justification required where this is not done. Whether this would be best achieved through legislative changes or updated guidance would need to be decided in consultation with key stakeholder groups.

⁹ Academy of Medical Sciences (2021). *Academy of Medical Sciences' response to the DHSC's Women's Health Strategy Call for Evidence*. <https://acmedsci.ac.uk/file-download/22836484>

¹⁰ Labots G, et al. (2018). *Gender differences in clinical registration trials: is there a real problem?* British Journal of Clinical Pharmacology **84(4)**, 700-707.

¹¹ Zucker I & Prendergast B (2020). Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of Sex Differences* 11, 32.

¹² Vitale C, et al. (2017). Under-representation of elderly and women in clinical trials. *Int J Cardiol* 232, 216-221.

In addition to reducing health inequalities linked to gender, there is an important role for regulators such as the MHRA in addressing the problem of exclusion of patients with multiple long-term conditions (MLTCs) from many clinical trials (OA1.3a, Academy of Medical Sciences' *'Cross-funder multimorbidity research framework'* (2019)).¹³ The Academy's 2018 report, *'multimorbidity: a priority for global health research'*, found that this exclusion is generally based on a belief that comorbid conditions may dilute or mask treatment benefits for the primary condition under investigation, or cause or exacerbate the side effects of the treatment under study. However, whether such concerns are justified is often not certain. Strict eligibility criteria that exclude those with common comorbidities mean that trial populations often do not include major subgroups of patients with the condition of interest, resulting in large differences between the study's population and the populations in which the evaluated treatment will ultimately be used. As a result, questions have been raised about the appropriateness of extrapolating data from some clinical trials to broader clinical populations with the target disease and comorbidities. In particular, the assessment of the balance of risks and benefits is often different in those with comorbidities compared to those with a single condition. Greater efforts are needed to include patients with multimorbidity in clinical trials.¹⁴ Participants at a FORUM workshop on *'multimorbidity: cross-sector opportunities for developing new interventions for patients with multiple long-term conditions'* noted that putting patients at the centre of clinical trial design and delivery (as proposed in question 1) could particularly benefit MLTC patients.¹⁵ To help improve the inclusion of MLTC patients in clinical trials, participants also recommended that the MHRA could co-develop a 'points to consider' guidance document for MLTC trials, which would act as the basis for discussions between regulators and sponsors about how MLTC are handled in regulatory submissions.¹⁶

Informed consent in cluster trials

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

Yes.

The Academy supports the timely move towards simpler, more proportionate procedures when seeking consent for low-risk trials in the NHS.¹⁷ However, the flexibility on consent issues should not be overdone. The risk is that too much flexibility might result in a situation where no consent is required where that would not be appropriate; a patient has a right to know when a clinician is making a treatment decision different from that they would normally make and a right to know when their data will be used for a clinical trial. Clarification about what the patient can and cannot consent to would be useful (e.g., they may not have a choice on which diagnostic test is used in a facility but might opt not to be followed up in a trial).

¹³ OA1.3a on page 5. Academy of Medical Sciences (2019). *Cross-funder multimorbidity research framework*. <https://acmedsci.ac.uk/file-download/49628715>

¹⁴ Academy of Medical Sciences (2018). *Multimorbidity: a priority for global health research*. <https://acmedsci.ac.uk/file-download/82222577>

¹⁵ Academy of Medical Sciences (2019). *Multimorbidity: Cross-sector opportunities for developing new interventions for patients with multiple long-term conditions workshop*. Monday 19 & Thursday 22 October 2020. <https://acmedsci.ac.uk/file-download/69473350>

¹⁶ Academy of Medical Sciences (2019). *Multimorbidity: Cross-sector opportunities for developing new interventions for patients with multiple long-term conditions workshop*. Monday 19 & Thursday 22 October 2020. <https://acmedsci.ac.uk/file-download/69473350>

¹⁷ The Academy of Medical Sciences (2014). *Response to the HRA consultation on seeking informed consent for simple and efficient NHS trials*. <https://acmedsci.ac.uk/file-download/34208-5476011fc9b91.pdf>

We heard of many examples where flexible, relevant, and proportionate consent requirements would be beneficial for participants and for the ability to generate reliable evidence with which to improve health. Examples include trials in which the timing, duration or frequency of existing treatments are being compared (e.g., 5-day compared to 7-day courses of antibiotics; 6 monthly compared to annual COVID vaccination) or where two licensed and widely used treatment regimens are being compared (e.g., aspirin compared to clopidogrel following a heart attack; heparin compared to aspirin for deep vein thrombosis prophylaxis). These are examples where both treatments are already widely used but there is variation in practice because there is no robust evidence about which approach is better (in terms of both efficacy and safety). Randomisation in a clinical trial may frequently be no higher risk than an arbitrary decision made by a health professional (but would have other benefits), so the process of randomisation (including consent) should be facilitated where possible to make it a more feasible option in more circumstances. Requiring full regulatory processes for such comparative effectiveness studies is disproportionate and they should be considered for simplified consent procedures; the requirements for consent should aim to be no more burdensome than the 'equivalent' consent process in routine care where there is no additional risk involved.

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

Yes.

The Academy supports the timely move towards simpler, more proportionate procedures when seeking consent for low-risk trials in the NHS,¹⁸ which can include cluster trials. However, we note that methodological approaches are not necessarily associated with certain levels of risks – for example, a cluster trial is not necessarily low-risk, and a non-cluster trial is not necessarily high-risk and may also benefit from a simplified, more proportionate consent procedure. In fact, we have heard that individual randomisation is generally more efficient, requiring fewer participants, and the findings are generally more valid. There is no reason to believe that removing the requirement for individual consent is more or less ethical in a cluster trial compared to an individually randomised trial. Therefore, it may also be worth considering if other trial types justify simplified consent procedures. (Please also see answers to questions 17 and 39.)

Safety reporting

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

Yes.

In general, the concept of aggregated reports at timely intervals is acceptable. It was noted that the requirement to report all SUSARs to all investigators is burdensome and receiving notification of individual cases without the wider emerging safety data may not be helpful. Removing this requirement is in-line with guidance issued by the US FDA. However, the value of reporting individual SUSARs to all investigators depends on the severity of a particular SUSAR. One of our Fellows was concerned that removing the requirement for individual SUSARs to be reported to all investigators at the earliest

¹⁸ The Academy of Medical Sciences (2014). *Response to the HRA consultation on seeking informed consent for simple and efficient NHS trials*. <https://acmedsci.ac.uk/file-download/34208-5476011fc9b91.pdf>

opportunity could put patient safety at risk, where a SUSAR is life-threatening or fatal; the Individual Brochure (IB) may not be regular enough to allay this risk.

We heard that when changes are made to the IB, the summary of changes provided to investigators are often brief, putting a burden on them to work through the IB and find more details, reducing compliance. If investigators are expected to rely on the IB to find out about SUSARs, it will be important to provide them with a meaningful summary of the changes, along with the new version of the IB, to reduce the administrative burden.

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

Yes.

Removing the requirement to report SUSARs and annual safety reports to RECs would remove a significant burden and bring the UK in line with FDA guidance. It should be noted that this would place reliance on MHRA, which would need to be adequately resourced to meet the demand.

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

Yes.

We have heard strong support for aggregate reporting of SUSARs. Guidance should be provided on when a sponsor would be expected to report an individual SUSAR (e.g., first time ever observed with this agent, high grade etc). Such guidance could be co-developed by MHRA and individuals/organisations with relevant experience and expertise, including statisticians, clinical trialists and investigators familiar with monitoring safety signals during ongoing clinical trials, patients, and those with academic and regulatory experience of investigating drug safety. (Such an approach was taken by the FDA in the last decade leading to significantly improved and well-reasoned guidance.) However, there is the potential for abuse and, as alluded to in the response to question 19, it will be vital that reporting of life-threatening or fatal SUSARs is not delayed by aggregate reporting. Furthermore, guidance should be provided on when a sponsor would be expected to report an individual SUSAR (e.g., first time ever observed with this agent, high grade). It was also noted that the definition of SUSARs is restrictive and can lead to overreporting of serious but inevitable events, such as death in a patient participating a trial for advanced cancer.

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

Yes.

Although there is some benefit of being able to see the totality of reports across multiple investigational sites, we have heard that, in general, listings of serious adverse events and serious adverse reactions in annual safety reports are of limited value and removal of the requirement will reduce administrative burden significantly. Inclusion of a discussion of signals and risks is more likely to educate and inform than the current system and we support legislative change should permit this. However, details should be left to guidance, which should be co-developed by MHRA and individuals/organisations with relevant experience and expertise (including statisticians, clinical trialists and investigators familiar

with monitoring safety signals during ongoing clinical trials, patients, and those with academic and regulatory experience of investigating drug safety).

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

Yes.

We agree that the proposal to extend the written notification for Urgent Safety Measures from no later than three to no later than seven days would be safe and easier to comply with, on the understanding that, as noted in the proposal, notification of the regulator by other means is expected to happen as soon as possible (usually via a phone call within 24 hours of the measure being taken).

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

Yes.

We agree that the proposed safety reporting requirements will reduce burden on researchers but maintain necessary levels of safety oversight as long as the concerns raised in the answers to questions 19 and 21 are addressed.

Good Clinical Practice

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

Yes.

We welcome the ambition to update the current GCP principles to ensure that they are proportionate and flexible and can be applied to a broad range of clinical trials. As technology, the NHS, and patient expectations change, the perception of proportionality will also change. Therefore, what is considered proportionate and 'fit for purpose' for researchers and regulators should be kept under active review. However, given that the revised principles are not specified anywhere in the consultation, it is difficult to comment whether they will adequately address the stated objectives.

To produce GCP principles that result in high-quality trials, a broader, adaptable framework to cover different trial types (e.g., adaptive trials) and research settings should be developed (rather than simply replacing ICH GCP (E6)),¹⁹ while retaining interoperability with ICH GCP. The development of updated GCP principles should be conducted in consultation with all relevant stakeholder groups, including patients, academics, funders, and policymakers.²⁰

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?

No opinion.

¹⁹ Academy of Medical Sciences (2018). Exploring Good Clinical Practice guidance in clinical trials – meeting summary. March 2018. <https://acmedsci.ac.uk/file-download/76367131>

²⁰ Academy of Medical Sciences (2018). Exploring Good Clinical Practice guidance in clinical trials – meeting summary. March 2018. <https://acmedsci.ac.uk/file-download/76367131>

Given the rapid growth of electronic data capture in medical research (and its major role in trials going forward), it is important that the electronic systems and data storage are of a high standard, and this should certainly be a feature of the revised principles. **However, the principles should be applied in a risk proportionate manner and there is strong concern that the current proposal, to apply GCP principles to all electronic systems that may impact on participant safety or reliability of results could have a negative impact on the use of clinical and other systems that is not risk proportionate.**

The current language, 'systems that may impact on participant safety or reliability of results', is too broad, including low-risk administrative systems such as those developed for clinical care or for collection and management of health records (e.g., those maintained by NHS Digital, the Office for National Statistics, the Clinical Practice Research Datalink, and similar bodies). Those systems are already governed by a combination of legislation, UK and international standards, and NHS (and other) policies. The revised principles could result in local hospital laboratory, electronic patient record or other systems being required to comply with GCP to be used for clinical trials, limiting selection of trial sites and worsening access to research for diverse communities. Layering on additional GCP requirements (which were not originally designed for, and are not necessarily fit for, this purpose) would not add value, either to the systems themselves or to the trial objectives. It would increase cost, reduce flexibility, impair innovation, and add burden in the UK that does not exist elsewhere in the world. **Therefore, it will be imperative to more narrowly define the electronic systems covered by the principles to ensure the impact is risk proportionate.** There also needs to be detailed guidance around how GCP is implemented to ensure a proportionate approach.

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

Yes.

As noted above in question 25, the proposed revised principles are not provided in the consultation and so it is difficult to assess whether they are appropriate and likely to deliver the stated objectives. For example, while the intent to 'ensure that Trial Master Files are proportionate and reduce the focus on extensive filing' is positive, we would need to see how the principles will be revised to deliver that to give a truly comprehensive answer.

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

All GCP principles are important and none of those we consulted made recommendations to remove any. Indeed, it is important that the UK does not adopt (or appear to adopt) a less stringent form of GCP, because data acquired in the UK in clinical trials is, generally, also submitted to regulatory agencies in other countries for product license approval. However, we have heard from a small number of our fellows that the language of many principles needs to be reworked to enable risk proportionality. The Good Clinical Trials Collaborative have developed a set of principles in consultation with around 100 people and organisations with experience or expertise in clinical trials from the UK and around the world, including patients, clinicians, ethicists, academics, biopharmaceutical and medical technology, medical research charities, government organisations, and regulators. These principles were based on ICH E6 (R3) and involved review of current UK legislation – they could present a good starting point for updating the current GCP principles.

We have heard that providing general GCP training for every clinician who may recruit somebody to a clinical trial is inappropriate, unnecessarily burdensome, and is preventing research being embedded into care pathways; particularly for trials of a low-risk

intervention or comparative effectiveness studies. Study-specific training should be adequate in most cases.

As a participant in a clinical trial, patients and volunteers do not have to pay for the investigational medicine they receive as part of the trial. To improve accessibility and avoid worsening inequalities, we agree that participants should also not be liable for treatment costs such as scans and consultations where a trial is being run by a private clinic, nor should a participant bear a financial cost to take part in a clinical trial.

Sanctions and corrective measures

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

Yes.

Taking into account information on serious and ongoing non-compliance that would impact participant safety when considering an application for a new study would be a reasonable way to prevent significant harm to participants. We have heard 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.

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

Yes.

Selective regulatory action that impacts part of a study, rather than the study as a whole, is appropriate in limited circumstances; patients who have already been recruited should not have their care interrupted or otherwise compromised unless absolutely necessary. Otherwise, where the regulator has significant concerns about part of the study, the sponsor should be required to provide urgent remedial action to allow another part of the study to proceed. Further guidance that ensures regulatory action is risk proportionate and effective should be co-developed between MHRA and those with relevant clinical trials experience or expertise.

Manufacturing and assembly

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

Yes.

The small number of our Fellows who commented indicated that introducing the term 'non-investigational medicinal product' into legislation is reasonable. However, it was noted that it would not be appropriate to apply the same GMP and GCP standards to these as to investigational medicinal products. Non-investigational medicinal products are typically given on prescription and would therefore be subject to the same quality and safety checks applied in routine NHS care.

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

Yes.

The small number of our Fellows who commented on this question agreed that removing the requirement for clinical trial-specific labelling (e.g., where normal or community pharmacy stock is used) would be sensible and would represent a significant resource saving. We have heard that it may also be appropriate to waive requirements around drug accountability for such medications, especially if the investigational medicinal product is being delivered via a standard prescription. Where clinical trial-specific labelling is required and a trials unit or general practice is holding a supply, the labelling should be allowable by medically qualified personnel at those sites as a matter of routine.

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

Yes.

We have heard general support from the small number of our Fellows who commented for the exemption of radio pharmaceuticals used in a trial from the need to hold a manufacturers authorisation of investigational medicinal products. However, the proposal text suggests that these sites will not need a manufacturing authorisation for the preparation of radio pharmaceuticals but would still need to be manufacture them to an 'appropriate level of good manufacturing practice', with the example given being a site that holds a manufacturing specials license. Further clarification is needed about what will be required of sites that manufacture and/or prepare radio pharmaceuticals (e.g., hospitals, health centres and clinics) to meet these expectations.

Definitions and other terminologies

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

We particularly welcome the proposal to use of 'participant' rather than 'subject'.

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

We welcome the intention to expand the groups of healthcare practitioners able to act as an Investigator in a trial, and we recognise the importance of explicitly defining which professional groups are included in the definitions of 'authorised health professionals' and 'health care professionals'. In addition to medical doctors and nurses, allied health professionals (e.g., radiographers, physiotherapists) should be able to be Investigators in relevant trials, provided they are fully trained. It is important that the decision about whether a particular individual is a suitable Investigator or Chief Investigator for a particular clinical trial should be determined by the GCP principle that 'each individual involved in conducting a trial should be qualified by education, training, or experience to perform his or her respective task(s).'

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

Yes.

The small number of Fellows who commented agreed that consent can be obtained by an appropriately trained and qualified member of the clinical team, which may mean nursing staff as opposed to a medical doctor; the GCP principle that 'each individual involved in conducting a trial should be qualified by education, training, or experience to perform his or her respective task(s)' applies. In routine clinical care and in many current clinical trials, this is the approach to consent for many procedures and treatments.

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

Yes.

Based on comments from a small number of our Fellows, we support the proposal for long term follow up in the form of data collection following the completion of trials, without the need for detailed medical approval where there is no ongoing administration of study treatments as part of the trial and participants will be under the usual care of the health services. The possibility of this could be included in the initial consent provided by trial participants at the outset. As mentioned in the answer to question 13, it would be beneficial if these changes could go further; in the context of data collection for long-term follow-up, the protocol and associated ethics approval needs to remain open/valid (so it is not appropriate to fully close the trial). However, since there is no ongoing administration of study treatments as part of the trial and participants will be under the usual care of the health services, such trials should be re-categorised as 'non-interventional'.

Conclusions

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

In general, we agree that the proposed changes will streamline clinical trials approval processes and remove unnecessary burdens to trial sponsors, though, as highlighted in previous answers, there are opportunities to streamline further while retaining and even improving patient safety. We welcome the intention to encourage both patient and public involvement (PPI) and support of diversity as this has the potential to greatly improve the quality of clinical trials performed in the UK. However, to fulfil the intention of streamlining processes and reducing bureaucracy, it will be critical to build in flexibility in recognition of the challenges in these spaces and avoid a tokenistic/box-ticking approach in areas like PPI. Furthermore, it will be crucially important to take an evidence-based approach in close consultation with stakeholders when developing legislation and guidance to avoid unintended adverse consequences. Building a world-leading regulatory science sector in the UK will be a priority for achieving such an evidence-based regulatory environment; during our recent workshop held jointly with the MHRA on '*advancing regulatory science for innovative medical products*', we were glad to hear the ambitions of the MHRA to become a global leader in this space.²¹

International compatibility of UK clinical trial legislation

The aim of this consultation to 'ensure legislation builds international interoperability so that the UK remains a preferred site to conduct multi-national trials' is welcome. Now that we are no longer part of the EMA system, MHRA market authorisation covers the UK

²¹ Academy of Medical Sciences (2021). Advancing regulatory science for innovative medical products workshop. Wednesday 3 March 2021. <https://acmedsci.ac.uk/file-download/10400150>

population of 70 million people, a small fraction of the 450 million people living in the EU. Therefore, there is a risk that companies may deprioritise seeking MHRA authorisation to access larger patient populations for their licensed medicines. Interoperability of UK clinical trials legislation with regulatory agencies of other countries – including the FDA, the EMA and similar – provides several advantages to increase the attractiveness of the UK as a place to run clinical trials, such as sped up assessment and adoption, preventing duplication of effort, and reducing the economic barriers to innovation by the private sector.²² We have heard that many of the proposals in this consultation bring UK clinical trials legislation in line with the regulatory guidance of other countries, including the FDA, and we also welcome the MHRA’s decision to join the Access Consortium.²³ Regulatory harmonisation provides a strong platform for international collaboration and commercialisation in health research. It is crucial that our regulatory systems continue to enable this collaboration and avoid creating unnecessary barriers.

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

The following areas (outlined below) should be considered: encouraging the reduction of the environmental impact of clinical trials; shortening and simplifying consent forms and patient information sheets; appropriately valuing patient reported outcome measures; ensuring regulation enables remote monitoring where safe and appropriate; remote monitoring and online trials; and the challenges of running clinical trials in primary care.

Environmental sustainability of clinical trials

We welcome the MHRA’s intention, stated in its consultation on *the future regulation on medical devices in the UK*, to become a ‘sustainability pioneer’. Many of the proposals in this consultation to streamline the regulation of clinical trials will likely indirectly reduce the environmental impact of clinical trials by eliminating unnecessary work. The upcoming changes to clinical trials legislation also present an opportunity to directly encourage the reduction of the environmental impact of clinical trials and medicines developed and used in the UK.

In the Academy’s response to the consultation on *the future regulation on medical devices in the UK*, we supported the proposals to require that manufacturers of medical devices complete an environmental and public health assessment.²⁴ Introducing waste management responsibilities into the medical device supply and reducing the environmental impact associated with a medical device will buttress the aim of the NHS to reach net-zero by 2045 and complement national healthcare sustainability initiatives such as the NHS Ocean initiative. As the Academy’s recent working group report with the Royal Society outlined, the NHS emits around 5-6% of the UK’s total greenhouse gas emissions and medicines and chemicals account for around 20% of NHS total carbon emissions (in comparison, medical equipment accounts for 10%).²⁵ Average CO₂ emissions generated by

²² Academy of Medical Sciences (2021). *Response to APPG on Access to Medicines and Medical Devices inquiry*. <https://acmedsci.ac.uk/file-download/38965811>

²³ MHRA (2021). *MHRA releases guidance in collaboration with Health Canada to improve patient safety in clinical trials through improving the quality of Development Safety Update Reports*. Published Tuesday 6 July 2021. [Last accessed Monday 07 March 2022]. <https://www.gov.uk/government/news/mhra-releases-guidance-in-collaboration-with-health-canada-to-improve-patient-safety-in-clinical-trials-through-improving-the-quality-of-development-s>

²⁴ Academy of Medical Sciences (2021). *Response to the MHRA consultation on the future regulation of medical devices in the United Kingdom*. <https://acmedsci.ac.uk/file-download/34065057>

²⁵ Academy of Medical Sciences & the Royal Society (2021). *A healthy future: tackling climate change mitigation and human health together*. <https://acmedsci.ac.uk/file-download/94272758>

a pragmatic randomised control trial from 2002-2003 in the UK was 78.4 (range 42.1-112.7) tonnes, which was an equivalent to that produced in one year by approximately nine people in the UK at that time.²⁶ There is evidence that these emissions can be significantly reduced by adopting strategies outlined in the NIHR Carbon Reduction Guidelines.²⁷ Therefore, introducing a similar requirement in the clinical trials and drug development space as the medical devices space to assess environmental impact could have a similar, or larger, impact on the carbon emissions of the NHS and the medical research sector as a whole and is worth consideration.

Shortening, simplifying, and improving the content of consent forms and patient information leaflets (not in the context of cluster trials)

While we welcome the proposals on simplifying consent for clusters trials and applaud the work in this area done to date by the MHRA,²⁸ further consideration of how to make consent forms and patient information leaflets accessible to patients while retaining the necessary level of detail for informed consent is needed for a broader range of trial types, particularly for low risk, primary care, and other studies. We have heard concerns that sick patients are unable to take on board the information in consent forms and patient information leaflets, which can be excessively long documents (up to 30 pages).

An overemphasis of the risks compared to the benefits of research participation in consent forms and patient information leaflets can cause people to miss out on the benefits of research participation. We have heard that a 'thick wall of warnings' often hides or overwhelms the positive aspects of research participation, which are often not as assiduously communicated. Furthermore, the focus on participation risks rather than potential benefits in consent forms and patient information leaflets may also be exacerbating the lack of diversity in participation in clinical trials; we have been informed of complaints from potential participants from ethnic minority groups who have been put off participating in research because of the emphasis on risks in the consent forms and patient information leaflets. Therefore, legislation to require communication of research benefits, in addition to risks, could be considered. This is consistent with the recommendation from our report on '*enhancing the use of scientific evidence to judge the potential benefits and harms of medicines*' that patient information leaflets should be revised in consultation with patients and carers to present a clearer, more simplified and balanced appraisal of the benefits and potential harms of the medicine.²⁹

Innovations to reduce trial participant burden - remote monitoring and online trials

There are ways to reduce the burden of monitoring calls, visits and tests on trial participants and sponsors. We have heard that, in trials investigating a medicine that is already licensed, there can be regulatory requirements for more tests and monitoring than is required for use of the drug in standard non-trial care, even if the drug is being used for the same indication and in the same population in the trial as outlined in the summary of product characteristics. This increases both the burden on trial participants and

²⁶ Lyle K, et al. (2009). *Carbon cost of pragmatic randomised controlled trials: retrospective analysis of sample of trials*. British Medical Journal **339**, b4187.

²⁷ NIHR (2019). *NIHR Carbon Reduction Guidelines*. Published Tuesday 30 July 2019. [Last accessed Monday 07 March 2022] <https://www.nihr.ac.uk/documents/the-nihr-carbon-reduction-guidelines/21685>; Subaiya S, Hogg E, Roberts I (2011). *Reducing the environmental impact of trials: a comparison of the carbon footprint of the CRASH-1 and CRASH-2 clinical trials*. Trials **12**.

²⁸ Academy of Medical Sciences (2017). *Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines*. <https://acmedsci.ac.uk/file-download/44970096>

²⁹ Academy of Medical Sciences (2017). *Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines*. <https://acmedsci.ac.uk/file-download/44970096>

sponsors. It should be acceptable for a trial to use monitoring calls, visits and tests conducted during the standard care of a patient; for example, using recent blood tests available from routine care testing rather than requiring new sets of bloods to be taken at study baseline. Furthermore, online and remote trials are becoming more common and much of this monitoring can be done at home by patients. Remote monitoring has huge potential to improve the efficiency and convenience of clinical trials while gathering meaningful real-world evidence, where used effectively.

Valuing patient reported outcome measures (PROMs)

While we welcome the intentions to further encourage PPI in this proposal, we have heard concerns that cultural attitudes of regulators and guidelines developers, which undervalue patient reported outcome measures compared to biological measures, could undermine the benefits of input from patients and the public. As stated in the Academy's response to the APPG on access to medicines and medical devices inquiry, in order to improve patient health and commission treatments of clinical value, it is critical to understand the needs and priorities of patients.³⁰ Historically, PROMs have been considered inferior to proximal or surrogate outcomes such as blood tests. However, there are cases where the most appropriate outcome is a PROM; for example, a recovery after an event, and in oncology, where outcomes other than overall survival are crucially important to patients.³¹ Given PROMs are frequently defined in consultation with patient and public contributors about outcome measures of critical importance to them, undervaluing them also undermines the importance of PPI input. By taking into account users' perspectives and ensuring that HTA is informed by the preferences and needs of patients, the quality, relevance and effectiveness of HTA can be enhanced. Biological measurements may have greater internal validity, and may be well suited to efficacy trials, but do not necessarily reflect the impact of an intervention in a real-world setting.

Considerations for clinical trials in primary care

While many clinical trials take place in a secondary care setting, there are many more potential sites in primary care; there are over 9000 general practice surgeries (GPs) in England. However, there are challenges to conducting primary care research. For example, GPs do not have access to a pharmacy that can supply trial drugs to participants. Some of the research done in primary care covers comparative effectiveness studies, and evaluations of medicines that already have a license, but where they might be considered for repurposing for additional indications. We would welcome amending regulations to allow community pharmacies to hold and distribute research medicines for community trials. Delivering study medication to participants homes in a way that is aligned to how medication might be issued and delivered if it were to prove beneficial in trials, has the additional advantage of trialling not only the treatment, but also its pragmatic implementation.

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

Introducing the concept of low interventional trials and risk proportionality in legislation will reduce the administrative burden on sponsors and the NHS, and therefore reduce associated costs. Allowing non-interventional follow up without regulatory approval could

³⁰ The Academy of Medical Sciences (2021). *Response to APPG on Access to Medicines and Medical Devices inquiry*. <https://acmedsci.ac.uk/file-download/38965811>

³¹ Academy of Medical Sciences (2017). *Looking to the future: oncology endpoints workshop*. Monday 03 July 2017. <https://acmedsci.ac.uk/file-download/41135280>

also be a huge cost saving for sponsors and the NHS. However, we have heard that the proposal to require (in law) direct access to the Trial Master File (TMF) for inspectors comes with significant costs (system and license fees, staff salaries, and information governance and cybersecurity risks).

It is acknowledged in the consultation that 'the advent of electronic Trial Master Files has introduced a complex and cumbersome filing system.' We welcome that the MHRA 'want to ensure that Trial Master Files are proportionate and reduce the focus on extensive filing'. However, the proposal to amend the legislation so that there is an absolute requirement that the TMF be 'directly accessible to MHRA inspectors' could be considered unhelpful. For many trials, the TMF is kept on secure internal systems (allowing compliance with data privacy and information governance requirements set by law and host organisation [e.g., university] policy). Altering information systems to allow direct access to the TMF for inspectors or purchasing new commercial electronic TMF systems (which can be very costly) seems unjustified, particularly as alternative methods to provide access to relevant information already exist and could be improved over time.

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

No opinion.

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

Yes.

Legislation to encourage meaningful PPI, as suggested in Section 3.1 (question 1), has great potential to indirectly increase the diversity of clinical trial participants. However, although we welcome the intention to directly improve diversity in clinical trials, the legislative changes proposed in Section 3.4 (question 16) are not comprehensive or detailed enough for us to fully support; there is the risk that the proposals could cause unintended adverse consequences and, if enshrined in legislation that is relatively difficult to modify, any unintended adverse consequences might be difficult to rectify. To avoid this, any changes should be evidence-based and determined in consultation with relevant stakeholder groups.

As mentioned in question 39, we have heard that a 'thick wall of warnings' often hides or overwhelms the positive aspects of research participation, which are often not as assiduously communicated. Furthermore, the focus on participation risks rather than benefits in consent forms and patient information leaflets may also be exacerbating lack of diversity in participation with clinical trials; we have been informed of complaints from potential participants from ethnic minority groups who have been put off participating in research because of the emphasis on risks in the consent forms and patient information leaflets.

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

The Good Clinical Trials Collaborative emphasised that:

'The design and implementation of clinical trials should recognise and be shaped by the characteristics of the settings in which they take place, including the health needs and

preferences of communities, and their understanding of clinical trials, as identified through appropriate patient and public involvement.'

This text could form a reasonable basis for an equality impact statement.

This response was prepared by Ania Kordala, Policy Intern, and Dr Anna Hands, Policy Officer, and informed by members of the Academy's Fellowship and previous policy work in this area. For further information, please contact Dr Anna Hands (anna.hands@acmedsci.ac.uk; +44(0)20 3141 3200)