**Proposals for legislative changes for clinical trials**

**Royal Pharmaceutical Society Response**

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, in general people involvement should be considered good practice and justification should be mandatory if not included similar to Paediatric Investigational Plans. However as very few people have lived experience of design, management and conduct of a clinical trial this would be an inappropriate requirement. Additionally, any legislation should not create hurdles compared with other countries around patient involvement as this may have a negative impact on the UK being selected for Clinical Trials.

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

Yes.

1. 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. In addition, the legislation should limit the length of the deferral and the number of time that deferment can be made. Consideration should be given to the potential impact on dissemination of results in medical journals which often (but not always) requires that the results have not been presented elsewhere which may disadvantage UK over other territories.

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

Yes. There should be a lay summary at a trial level perhaps on a relevant registry and the investigator should have the option to discuss individual results with the participant. Direct sharing of results with participants would put a significant resource burden on the trial sites involved. An example of where this becomes difficult could be in long term oncology studies it may be very difficult and upsetting if they are reaching out to families of deceased patients to alert them to the results of the trial overalls as such there should be an ‘opt out of results’ aspect, and a method to handle reporting to bereaved where findings are shared.

1. 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.

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

Yes.

1. 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.

1. 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. but only in exceptional circumstances. Dependent on the trial design, investigational product and method of manufacture (g POC Manufacture) it would be appropriate for other experts to be included in the review. This timeframe needs to be defined and the knowledge of what is in development should help MHRA in having ready access to a panel of experts for specific diseases and manufacturing.

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

Yes. Given this atypical approach, communication with all interested parties will be paramount to safe implementation, please consider mechanisms to ensure communication to trial sites.

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

Yes, the detail in schedule 3 is more appropriate as guidance because there needs to be some flexibility in the detail. however the requirement to produce documents should be in legislation and clear guidance that patient facing documents are visible to the REC.

1. 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

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

Yes

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

Yes. The legislation would need to clearly specify the criteria that must be met for a trial to fit within the notification scheme, so trial sponsors have confidence their trial complies with the legislation

1. 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

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

The REC should continue to have a balance of lay and expert members, and this should be specified in legislation

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

No. Guidelines to support diversity are more appropriate than legislative requirements. It is a complex area with cultures and beliefs to be respected but also medical contra indications (by age, ethnicity etc.). Legislation could state that both sponsors and investigators need to take measures to enable equal access to clinical trials to all (including minority groups e.g. ethnicity, gender, age, and other). It would be beneficial to understand the MHRA’s aim in terms of diversity – racial and ethnic minority goals, health equity or patient engagement strategies. Also, important to consider the broadest definition of diversity and how this could align with the Governments levelling up agenda.

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

We agree with the caveat that the person who will be participating in the trial is made fully aware of what is happening and the fact that they will be part of a trial and their data shared for his purpose – and that they then consent to this.

1. 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

1. 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

1. 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

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

Yes, but the level of reporting should be proportional to the risk of product i.e. stage of development of the product and population it is trialed in.

1. 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, because the discussion of signals/risks and the proposed mitigation actions would highlight the SAE/SARs which would already have been reported. However there needs to be a system in place that if there were such changes required to the IB that these would be communicated in a timely manner to relevant parties.

1. 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, amending written notification for urgent safety measures to no later than 7 days from when the measure was taken would be more practical.

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

No. Not for higher risk products (e.g., those in early development) The level of reporting should be proportional to the risk of product as there are concerns that if the appropriate reporting for that IMP and participant population were not undertaken in a timely manner that this might jeopardise participant safety if the right degree of oversight is not in place.

1. 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. For non-commercial sponsors delivering trials in the UK, the introduction of a risk proportionate approach is generally considered as welcoming. Further guidance and exemplars how proportionality could be applied in practice would be required to facilitate a culture of trial conduct that is proportionate.

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

Yes

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

Yes

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

The principles of informed consent are to include details of the trial and the manufacture of the IMP. Also, patient protection should be paramount, and it is important to be included, so that the patients are fully informed.

1. 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?
2. 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

1. 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?

No, auxiliary medicinal product terminology more appropriate as NIMP term can be confusing.

The proposed term ‘non-investigational medicinal product’ is confusing when the intention is to also include products which are non-medicinal products. Would the term ‘non-investigational product’ be more appropriate? Confusions between NIMP and concomitant medications have also been noted in practice; the definition needs more clarification to enable effective implementation.

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

Yes, however the legislative text would need to include an emphasis on risk assessment rather than solely based on the marketing authorisation of a product. The inclusion of specific clinical trial labelling can sometimes be helpful to facilitate product accountability and timely reporting of serious adverse reactions. The impact of PIL in approved packaging on reporting of adverse drug reactions as the medicine may be used with other medication which could cause unintentional side effects must also be considered. As such, the risk assessment should have a wider scope. (For example, considering the mechanism of supply as in secondary care- dispensing label would be applied and PIL could be removed at that stage). There needs to be greater transparency on risk assessment carried out by sponsors.

1. 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, in some circumstances. This would be welcomed for manufacture of some diagnostic radiopharmaceuticals, although there are instances where we believe MIA(IMP) and QP certification would still be required. For example, an exemption would be of benefit and appropriate to those radiopharmaceuticals manufactured using a Radionuclide generator to radiolabel a freeze-dried cold kit. For other radiopharmaceuticals, largely those produced via a cyclotron, we believe there is a higher risk due to the complexity of the manufacturing process, number of critical controls, extensive validation, and degree of product characterisation required. It is our opinion that it is not appropriate for an MIA(IMP) exemption for radiopharmaceutical manufacture of this type for use in a clinical trial.

In addition, we seek clarity as to whether radiolabelling is a manufacturing or reconstitution activity. If it considered to be manufacturing, then a specific exemption for radiolabelling to enable it to be performed without an MIA(IMP) in a suitably competent facility (such as those with an MHRA MS or those subject to EL97(52) audits). If it is considered preparation, it is clear that this is not licensable, however in both scenarios there may be the need for annex 13 labelling. This should be defined

We also feel this exemption radiolabelling cold kits using a radionucleotide generator should not be limited to licensed starting materials but should include materials that have been manufactured under an MIA or MIA(IMP) and QP certified. This will be key to increasing the capacity for delivery of Clinical Trial, while maintaining the principles of quality, safety and efficacy.

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

This presents an opportunity to review the overlap which occurs between GMP and GCP inspections of a company/sponsor. GMP inspections provide assurance that the site where IMP is manufactured/manipulated/certified for release by a QP is suitable and the PQS supporting all activities undertaken is appropriate. It therefore introduces inefficiencies within both the MHRA and for companies when GCP inspectors spend time asking questions about the quality and suitability of the IMP being used in a specific trial. Some alignment and coordination between these two compliance groups would be appreciated by all.

This change in legislation is an opportunity to broaden the scope of the Regulation 37 exemption to permit labelling by registered healthcare professionals, not only pharmacists. This would be helpful in NHS settings for radiopharmaceutical and ATMPs where delays can occur due to current requirements which are not commensurate to the risk given the skill and registration of those performing the tasks.

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

Suitably qualified and Trained AHPs such as Pharmacists or Research Nurses. Consideration should be given to individuals who are independent prescribers or authorised health professionals who are legally permitted to supply/administer a restricted list of medicines without a prescription, where such list contains the IMP in question (e.g. trials which are comparing two drugs which are both routinely used in clinical practice). However, emphasis should be placed on the individual’s scope of professional practice and competency. In addition, a key consideration should be the level of risk associated with a trial (e.g. early phase trials are likely to be associated with a higher risk).

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

Yes. Further guidance would be required on what would be considered as “appropriately trained” and “qualified member” to facilitate implementation in practice.

1. Do you consider it appropriate that data collection following MHRA approval for use of an unlicensed medicine can be considered as noninterventional where the collection is according to the ‘approved’ use?

Yes. These noninterventional trials would still need to be regarded as research studies requiring REC approval.

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

Yes

1. 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?

* Inspection considerations- GCP vs GMP. These regulatory inspections often overlap. Clearly defined standards for inspection would improve efficiency.
* Regulation 37 review specifically for assembly permitted “(ii)by a doctor, a pharmacist or a person acting under the supervision of a pharmacist;”. It is recommended this is amended to registered healthcare professionals when working under GMP in areas such as nuclear medicine and cellular therapies.
* Mandating the new National Contract
* Serious breach legislation should be included.
* Inclusion of specific reference to Decentralized Clinical Trials
* Inclusion of specific reference for complex trials
* It is important that the new legislation does not impact the current desirable accessibility to the CTU at the MHRA

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

If risk proportionality is applied and applications can be made more “fit for purpose” both regulators and regulated should benefit from a time/cost reduction in the preparation and review of applications. If the process of regulating trials can be further streamlined, more companies will wish to undertake studies in GB. In the past this was clearly demonstrated when the succinct critical summaries were introduced for CTAs, replacing lengthy individual reports required by other countries.

1. We do not consider that our proposals risk impacting people differently with reference to their protected characteristics or where they live in NI. We welcome any further views on this point

References to DCTs would support a more rural CT landscape by reducing or eliminating the need to travel to specific sites improving accessibility to patients

1. 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.
2. Do you have any evidence that we should consider in the development of an equality assessment?