EXPLANATORY MEMORANDUM TO

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) (AMENDMENT) REGULATIONS 2024

2024 No. [XXXX]

1. Introduction

1.1 This explanatory memorandum has been prepared by The Medicines and Healthcare products Regulatory Agency ("MHRA"), an executive agency of the Department of Health and Social Care ("DHSC") and is laid before Parliament by Command of His Majesty.

1.2 This memorandum contains information for the Joint Committee on Statutory Instruments.

2. Declaration

2.1 Baroness Merron, Parliamentary Under-Secretary of State for Patient Safety, Women's Health and Mental Health, confirms that this Explanatory Memorandum meets the required standard.

2.2 Harriet Teare, SCS1 for Partnerships, at the MHRA confirms that this Explanatory Memorandum meets the required standard.

3. Contact

3.1 Partnerships Team at the Medicines and Healthcare products Regulatory Agency, email: Partnerships@mhra.gov.uk, can be contacted with any queries regarding the instrument.

Part One: Explanation, and context, of the Instrument

4. Overview of the Instrument

What does the legislation do?

4.1 This instrument amends the Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I. 2004/1031) ("the 2004 Regulations") to reform the UK legislation for Clinical Trials, responding to the needs of the sector to deliver a more streamlined and flexible regulatory regime, whilst protecting the interests of trial participants.

4.2 The amendments will:

- promote public health and ensure protection of participants remains at the heart of legislation
- facilitate the evaluation and development of new or better medicines to benefit patients and society
- remove obstacles to innovation, whilst maintaining robust regulatory oversight of the safety of clinical trials
- streamline the regulation of clinical trials and reduce unnecessary burden to those running clinical trials by taking a risk-based approach
- ensure the legislation enables clinical trial sponsors to work across countries so that the UK remains a preferred site to conduct multi-national trials.

Where does the legislation extend to, and apply?

4.3 The extent of this instrument (that is, the jurisdiction(s) which the instrument forms part of the law of) is the whole of the United Kingdom.

4.4 The territorial application of this instrument (that is, where the instrument produces a practical effect) is the whole of the United Kingdom.

5. Policy Context

What is being done and why?

5.1 This instrument reforms the clinical trial regulations to deliver a more proportionate, streamlined and effective clinical research environment, ensuring the UK is at the forefront of innovative regulation for clinical trials whilst protecting the interests of trial participants. This instrument will amend provisions relating to the authorisation and conduct of a clinical trial, research ethics, safety reporting of a trial, and the manufacturing and labelling of the medicine being investigated within the trial.

Approval of Clinical Trials

5.2 The provisions in this instrument are intended to simplify and streamline the process for approval of clinical trial applications, making it easier to apply for trials in the UK but without compromising on safety standards.

Combined Review

5.3 To run a clinical trial a sponsor (the individual or organisation with responsibility for the trial) must obtain regulatory and ethics committee approval. The ethics committee review safeguards the rights, safety, and well-being of people taking part in clinical trials. The regulatory review ensures the safety of the clinical trial and the safeguarding of clinical trial participants. The 2004 Regulations outline that the application for a clinical trial regulatory authorisation is separate to an ethics committee favourable opinion and both processes are set out separately.

5.4 In 2018, the MHRA and the Health Research Authority ("HRA") successfully piloted a combined review process, which became the exclusive route for clinical trial applications from January 2022. It offers a single application route and co-ordinated regulatory and ethics committee review leading to a single UK decision for a clinical trial. This instrument embeds the combined approval process into legislation. The review timelines will also be updated to ensure flexibility and competitiveness. Following a 7-day validation period, applications will be reviewed within a maximum 30 calendar days, with a maximum 10 calendar days for a decision to be granted once the regulator and/or ethics committee has received responses to any Request for Further Information ("RFI").

5.5 Requests for Further Information are issued by the MHRA and/or ethics committees to a trial sponsor if a clinical trial application does not have sufficient information to allow an approval, or where changes to the submitted information are needed. This instrument will introduce greater flexibility to the formal communication between applicants and regulators during the process of requesting this information. Sponsors will now have 60-days (increased from the current 14-days for standard applications) to respond to an RFI, to facilitate the harmonisation of international protocols and better align requests for changes from multiple regulators. The sponsor has the ability to respond very rapidly where appropriate, or to use the additional flexibility to allow them adequate time to develop robust responses to any questions.

5.6 After approval of a clinical trial has been given, if the sponsor wants to change any aspect of a trial that may have a substantial impact on the safety of trial participants or on the reliability and robustness of the data generated, then a substantial modification is required and must be submitted for approval. Currently, substantial modifications can only be approved or rejected. This instrument will include provisions for the ability to receive an RFI during the review of substantial modifications. This will help streamline the current process and avoid rejections that may cause delays or interruptions to an ongoing trial.

Notification scheme

5.7 This instrument embeds a notification scheme for both initial applications and modifications into legislation. A similar scheme currently exists in guidance for initial applications, which sponsors may opt to follow. This new approach is based on the principle of risk-proportionality and will reduce the time to get lower-risk clinical trials up and running without undermining patient safety.

5.8 To protect participant safety, clinical trials where there is a significant safety concern with the product will not be eligible for notification. Clinical trials that meet the criteria for notification will receive an automatic authorisation from the licensing authority, which will then feed into the combined decision to the sponsor. An ethics committee favourable opinion will still be required before the clinical trial can begin. The sponsor will be responsible for determining that the clinical trial meets the eligibility criteria for notification, which will be clearly outlined in the legislation.

5.9 A substantial modification would be either a Route A or Route B substantial modification. For Route A substantial modifications, both the licensing authority and ethics committee will need to review the request in order to provide a decision. Where a modification meets the criteria of a Route B substantial modification, that modification will receive an automatic decision from the licensing authority. If the modification relates to the ethics committee as well, then the ethics committee opinion will still be required before the sponsor can proceed with the modification. The sponsor will be responsible for determining that the modification meets the eligibility criteria for a Route B substantial modification, which will be clearly outlined in the legislation.

5.10 Additionally, modifications to clinical trials which the regulator and ethics committee would need to be aware of for administrative or oversight purposes, but do not impact the safety or rights of the participants, will also be notified and can proceed without an approval.

Research Ethics and Research Transparency

5.11 Research ethics review is carried out by ethics committees and a clinical trial requires a favourable ethics committee opinion before it can begin. The 2004 Regulations set out a Schedule of very specific, restrictive and granular provisions on the make-up, proceedings, support staff, premises and facilities relating to ethics committees. This Schedule will be removed and will be replaced with a new provision on how an ethics committee should be constituted, aligning with international good clinical practice standards, alongside an expanded provision for the United Kingdom Ethics Committees Authority to establish and abolish ethics committees.

5.12 This instrument makes new provisions to promote transparency and public access to information about clinical trials. It sets in legislation expectations that are currently outlined in guidance by requiring the registration of trials in a public registry before recruitment of the first participant or within 90 days (whichever is sooner),

publication of a summary of results in the same registry within 12 months of the conclusion of the trial, and the offer to participants (or other relevant persons such as a parent or a legal representative) a summary of the results written in a manner that is understandable to laypersons.

5.13 Sponsors may request a deferral of these transparency requirements for up to 30 months from the conclusion of the clinical trial, for example to protect commercially confidential information. A waiver may also be requested in exceptional circumstances, for example, in matters relating to national defence and security. Phase I trials may receive an automatic deferral from transparency requirements, provided that certain essential information is registered. Further deferral requests can be made before the previous deferral expires, but the cumulative deferral period must not exceed 10 years from the conclusion of the clinical trial.

Conduct of Clinical Trials

5.14 The 2004 Regulations outline how a clinical trial must be conducted in accordance with Good Clinical Practice ("GCP") to ensure the safety of participants and integrity of the data generated. GCP is a globally recognised set of expectations and is set out in the International Council for the Harmonisation (ICH) Guidelines on GCP, which are currently undergoing a revision. This instrument updates the provisions on GCP to align with the principles of the ICH guidelines and to ensure continued alignment in the future. This will ensure that clinical trials conducted in the UK continue to meet international standards, enabling international interoperability and global acceptance of UK clinical trial data.

5.15 This instrument also updates the provisions relating to the suspension or termination of a clinical trial. The 2004 Regulations allows for a clinical trial authorisation to remain valid indefinitely, even though medical practice may change over time. This instrument introduces a 2-year time limit after which the clinical trial approval will lapse if no participants have been enrolled, with the possibility for extension if agreed with the regulator and ethics committee. The 2004 Regulations only allows for regulatory action to be taken against a whole trial, which does not reflect modern clinical trial design or enable proportionate regulatory activity. This instrument therefore provides for regulatory action to be taken against a specific part of a trial where appropriate, rather than necessarily needing to be taken against the whole trial.

5.16 This instrument will enable simplified arrangements for obtaining and evidencing consent (supported by detailed guidance) for lower-risk clinical trials involving authorised medicines that pose minimal risk for participants. This includes cluster trials involving randomisation to an authorised medicine pre-determined by group or location. This will promote proportionality, allowing potential participants to receive adequate information about the clinical trial while enabling them to provide consent through an easier process.

5.17 Where justified and agreed, simplified consent arrangements may be used for clinical trials where:

- the investigational medicinal product(s) is authorised for use in the United Kingdom and is used in accordance with that authorisation; and
- the investigational medicinal product(s) is provided as part of routine care; and
- the participants receive no additional medication(s) or undergo additional procedures solely for the purposes of the trial.

5.18 Sponsors will be required to provide the reason for using simplified consent arrangements, the information provided to participants, how it is provided and how consent will be documented.

Safety Reporting

5.19 This instrument will update the pharmacovigilance aspects of clinical trials, aimed at reducing administrative burden, while maintaining the highest standards of patient safety.

5.20 Sponsors of clinical trials need to identify Suspected Unexpected Serious Adverse Reactions ("SUSARs"), which are serious adverse events suspected to be caused by the medicinal product under investigation. These must be reported in an expedited manner to the MHRA on an individual basis. This instrument will remove the legislative requirement for sponsors also to directly report SUSARs to investigators and to ethics committees, removing a duplicative legislative requirement. Sponsors will also be able to assess the causality of some serious adverse events by reviewing cumulative data rather than single occurrences.

5.21 Sponsors prepare safety reports on an annual basis to reassure the regulators that they have adequate oversight of the safety profile of the investigational drug. However, the reports currently submitted to regulators are not transparent because they contain listings of all individual serious adverse events and reactions without a description of how they have been evaluated and interpreted. This instrument will update the annual safety reporting expectations, stating that sponsors should provide a report setting out signals/risks associated with the use of the medicinal product. This will include mitigation actions that have been taken.

5.22 Lastly, this instrument will update the provision that sets the timeline for written notification of Urgent Safety Measures ("USMs") from 3 days to 7 days. USMs are reported to the MHRA after they have already been implemented and actions have been taken to protect the safety of trial participants. The added time for written notification of the measure taken can be used to gather data that will facilitate the regulatory assessment of the measures. In addition, this change supports international harmonisation because similar measures are in the European legislation.

Manufacturing and Labelling of Investigational Medicinal Products

5.23 The updates to legislation will include a thorough definition of 'non-investigational medicinal products' ("NIMPs"). These are secondary products that are used to support a clinical trial, whilst not being the investigational medicinal product. NIMPs are currently defined in UK guidance; they are not a new concept. This definition will provide assurance of the quality and safety of these products, especially where products are being used that may currently be unregulated. An example of this is challenge agents, secondary products that are given to clinical trial participants to produce a bodily response that is necessary prior to the investigational medicinal product ("IMP") being assessed.

5.24 Currently, radiopharmaceuticals used for diagnostic purposes in a clinical trial require a specific Manufacturing Authorisation for an Investigational Medicinal Product ("MA IMP"). Under the amendments made by this instrument, radiopharmaceuticals which are used exclusively at a trial location (in a hospital or health centre), will require a valid manufacturing licence, but it will not need to be specific to IMPs. Manufacturers will still need to comply with Good Manufacturing Practice to continue to assure the safety and quality of those products.

5.25 This instrument will also introduce greater flexibility in the requirements for labelling clinical trial medicines. Where a medicine is labelled according to its marketing authorisation ("MA"), and certain conditions are met, the legislation will allow for medicines to be used with just their MA labelling, rather than specific clinical trial labelling. All information already on the licensed packaging will still be required in the majority of cases. The risk-proportionate approach will reduce duplicative labelling in certain situations, for example where the medicine remains at the trial site and is not taken away by a participant or where a medicine is administered at the trial site, as a single dose by a healthcare professional.

What was the previous policy, how is this different?

5.26 The current legislation was based on the EU Clinical Trials Directive (2001/20/EC). The legislation included a large amount of detail and duplicative requirements which placed an administrative burden on the sponsor. Following exit from the EU, there was an opportunity to reform our national legislation to deliver a world-class sovereign regulatory environment for clinical trials to support the safe development of innovative medicines for the benefit of patients and public health.

5.27 The new legislation will streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk proportionality, and promote involvement in clinical trials.

6. Legislative and Legal Context

How has the law changed?

6.1 The Medicines for Human Use (Clinical Trials) Regulations 2004 set out the regulatory regime for clinical trials in the UK. The framework provides a scheme for regulating clinical trials of medicines involving humans that covers the authorisation of clinical trials, their ethical approval, the conduct of the trial including adherence to good clinical practice, the reporting of adverse events and breaches of the authorisation, the manufacture and importation of the medicinal products involved in the trial and their labelling. The regulatory regime is overseen by the UK licensing authority operating through the MHRA and the HRA with the UK Research Ethics Service.

6.2 The current regulatory regime was based on the EU Clinical Trials Directive (2001/20/EC), which has been repealed and replaced by a new EU Clinical Trials Regulation 536/2014.

6.3 The Medicines and Medical Devices Act 2021 ("MMD Act") provides enabling powers to make provisions amending or supplementing the "law relating to human medicines", which includes the 2004 Regulations, as well as the power to make provision "corresponding or similar to provision in the EU Clinical Trials Regulations".

Why was this approach taken to change the law?

6.4 This is the only possible approach to make the necessary changes.

7. Consultation

Summary of consultation outcome and methodology

7.1 Section 45 of the MMD Act requires that, before making regulations under section 2, a public consultation must be carried out. As part of the development of the proposals

being given effect to by this instrument, a public consultation was carried out from 17 January to 14 March 2022. The consultation received 2,138 respondents, 88% from individuals and 12% from organisations. Individual responders included members of the public, patients, carers, researchers, and healthcare professionals. Organisational responses came from industry trade associations, academic institutions, individual pharmaceutical companies, not for profit organisations involved in drug development, patient advocacy groups, regulatory/ professional representation bodies and health delivery organisations.

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

7.3 Feedback on each proposal was carefully considered and following analysis of the consultation, it was decided that four of the initial proposals would not be taken forward. Proposals were also adapted following the analysis of feedback.

7.4 A summary of the consultation responses and the Government's response can be found here: Government response - Consultation on legislative proposals for clinical trials[1].

7.5 Following the publication of the government response to the consultation, a series of well-attended workshops have been held with a range of relevant stakeholders to ensure continued support of proposals and to develop additional detail.

7.6 This instrument is being made on a UK-wide basis. The Devolved Administrations have been consulted on the development of this instrument. The regulation of medicines is a devolved matter for Northern Ireland. This instrument has therefore been made jointly with the Northern Ireland Department of Health, and the public consultation was also carried out jointly.

8. Applicable Guidance

8.1 Detailed guidance will be provided by the MHRA and the HRA in advance of the regulations coming into force.

Part Two: Impact and the Better Regulation Framework

9. Impact Assessment

9.1 A full Impact Assessment has not been prepared for this instrument because there will be a low level of impact per business. The analysis of the impact on businesses has been completed and a De Minimis Assessment and Equality Impact Assessment will be published alongside the Explanatory Memorandum on the legislation.gov.uk website.

[1] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1144407/Clinical_Trials_Final_government_response_to_consultation.pdf.

Impact on businesses, charities and voluntary bodies

9.2 The impact on business, charities or voluntary bodies is estimated to cost approximately £1.2m with expected benefits of approximately £9m over the next ten years to the sector. Other wider impacts include the benefits from better transparency measures for participants in clinical trials and better risk proportionality to ensure regulatory requirements best reflect the risks a trial could pose to participants.

9.3 The legislation does impact small or micro businesses.

9.4 Small or micro businesses are not expected to experience disproportionate impacts in comparison to medium and large businesses. This is because they generate 1% of the total turnover in the sector, although they account for 56% of the biopharmaceuticals sector. Furthermore, the legislative amendments aim to make regulation of clinical trial protocols more efficient, which will include key benefits that small and micro businesses would gain from. Therefore, they are not exempted from the requirements of regulation.

9.5 All values are in 2019 prices, with 2020 present values. All values are rounded to two significant figures.

9.6 There is no, direct monetary cost impact on the public sector because the amendments to the current legislations are primarily designed to improve regulatory oversight on trial sponsors. However, the wider impacts on the public sector include easier access of participants and the public to clinical trial outcomes through better transparency measures, enhanced safety in clinical trial protocol for participants through better risk proportionality measures.

10. Monitoring and review

What is the approach to monitoring and reviewing this legislation?

10.1 DHSC and the MHRA will keep the impact of the policy under review. In addition, section 46 of the MMD Act 2021 requires the Secretary of State to lay a report before Parliament every two years on the operation of regulations made under section 15 (and other powers under the Act). There is also a requirement, prior to producing the report, to consult with relevant stakeholders and gain their feedback on how the regulations are operating.

10.2 The instrument does not include a statutory review clause and, in line with the requirements of the Small Business, Enterprise and Employment Act 2015, Baroness Merron has made the following statement:

"It is not appropriate in the circumstances to make provision for review in this instrument. This is because there is already a requirement in section 46 of the Medicines and Medical Devices Act 2021 to review the operation of these Regulations every 24 months".

Part Three: Statements and Matters of Particular Interest to Parliament

11. Matters of special interest to Parliament

Matters of special interest to the Joint Committee on Statutory Instruments

11.1 This instrument is made under the Medicines and Medical Devices Act 2021. It amends The Medicines for Human Use (Clinical Trials) Regulations 2004, which were made under section 2(2) of the European Communities Act 1972. This instrument is subject to the draft affirmative procedure in accordance with section 47(3) and 6(c) of the Medicines and Medical Devices Act.

11.2 There is reference to the International Council for the Harmonisation (ICH) Guideline on Good Clinical Practice, as amended from time to time. This ambulatory reference is there because the ICH guideline is undergoing change, and the Regulations need to keep up with changes to the ICH Guideline. The EU Clinical Trials Regulations also refers to the ICH guideline and does not specify a date for the guideline. Additionally, the Medicines and Medical Devices Act 2021 provides an enabling power to make provision "corresponding or similar to provision in the EU Clinical Trials regulations". Therefore, in this instrument, the reference to the ICH guideline "from time to time" is not in reliance on a power to make ambulatory reference, but rather in reliance on the power to make corresponding or similar provision to the EU Clinical Trials Regulations.

11.3 There are two provisions being amended by this instrument which are also being amended by the Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2024 ("POC Regulations"). These are to Part 7 and regulation 48(4) of the Medicines for Human Use (Clinical Trials) Regulations 2004, which are both being replaced by this instrument. The POC Regulations were laid very recently on 21st October 2024, and the debates will likely follow the usual timetable in Parliament and the NI Assembly. The POC Regulations have not yet been made at the date of laying this instrument, and it is likely that this instrument will be made last. If that is the case, this instrument needs to incorporate the amendments made by the POC Regulations on those two overlapping provisions, so that the law is in its final form when this instrument is made. Therefore, this instrument includes the changes made by the POC Regulations to Part 7 and regulation 48(4). Part 7 has been amended to include provisions that achieve the same policy objective as the amendment made by the POC Regulations to this Part, and regulation 48(4) has been amended so that it includes the reference to regulations 36A and 36B which are being inserted by the POC Regulations. These amendments are based on the assumption that the POC Regulations will be approved by Parliament and the NI Assembly and made into law before this instrument. If the POC Regulations are not approved and made into law first or at all, then this instrument will need to be amended accordingly.

Matters of special interest to the Northern Ireland Assembly

11.4 Section 2(6)(b)(ii) of the Medicines and Medical Devices Act 2021 provides that, in relation to Northern Ireland, regulations under section 2 may be made by the Department of Health in Northern Ireland and the Secretary of State acting jointly. This instrument will apply to the whole of the United Kingdom and accordingly is made jointly.

11.5 Section 47(6)(c) of the Medicines and Medical Devices Act provides that in the case of the regulations being made jointly, the regulation must be laid before and approved by a resolution of each House of Parliament and the Northern Ireland Assembly.

12. European Convention on Human Rights

12.1 Baroness Merron made the following statement regarding Human Rights:

"In my view the provisions of The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2024 are compatible with the Convention rights."

13. The Relevant European Union Acts

13.1 This instrument is not made under the European Union (Withdrawal) Act 2018, the European Union (Future Relationship) Act 2020 or https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1144407/Clinical_Trials_Final_government_response_to_consultation.pdf the Retained EU Law (Revocation and Reform) Act 2023 ("relevant European Union Acts").