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FPM Consultation on the MHRA's draft guidance on Clinical trials for medicines

Guidance: Please respond to each question to the best of your knowledge within this document. Please provide your name alongside your comments. The completed document will then be circulated to the FPM PCG and any pertinent internal stakeholders (other contributors) for review.

Title of Consultation: Draft guidance on Clinical trials for medicines

Organisation: MHRA

Submission Deadline: 5PM Friday 17th January 2025

FPM Review Deadline: EOD Monday 13th January 2025

Consultation Summary:

New Clinical Trials legislation was laid in UK Parliament on 12 December 2024 that will address the research sector's need for a more efficient, streamlined and adaptable regulatory framework for clinical trials.

Once made into law, the new legislation will come into force following a 12-month implementation period to ensure readiness.

During this implementation period, the MHRA are sharing draft guidance for review by subject matter experts, key stakeholders and future users.

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Questions:

1. Would any additional diagrams be useful? If so, please describe the relevant area(s), referencing section titles where possible.

- Yes
- No

Relevant areas (optional):

A flow diagram for the expert review process from line 418-465 would be helpful to clarify the timelines involved.

2. Is the language used in the guidance accessible and easy to understand?

- Yes
- No
- Uncertain

If no, please provide a short explanation as to why (optional):

Some cross-references to other parts of the document are unclear, so we should add the location, and some external references need more clarity (e.g. notifiable trials in line 112 are not explained until line 466). Also, some examples of exceptional circumstances in line 45 would be helpful.

3. With reference to lines 23 to 373, is the guidance clear on how to apply for clinical trial approval (excluding applications made through the notification scheme)?

- Yes
- No

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If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

As mentioned above - the overall notification is clear, but the notifiable trials aspect is not detailed until much later. Also, approval with conditions is not clear on the first read, whether there is a requirement for notification (not for approval) at the time of fulfilling conditions before or at the time of the study's start.

4. With reference to lines 23 to 373, is there any information missing that would help your understanding of the process of applying for clinical trial approval (excluding applications made through the notification scheme)?

- **Yes**
- **No**

If so, please describe this information (optional):

It would be helpful to clarify whether information about approval with conditions (line 74) needs to be included in the DSUR, as this is referenced much later in the guidance. Additionally, in line 201, guidance on how open-label extensions, safety follow-up studies/extensions, and compassionate or extended use post-study are managed should be provided.

There is no mention of the ability to cross-reference to the IB for the preclinical and clinical parts of the IMPD (previously noted in CT-1 paragraph 84). While it is presumed this is still possible, the lack of an explicit statement could cause confusion for applicants. This clarification should be added to the cross-referencing section starting at line 306.

Finally, providing examples of conditions of approval for each of the three disciplines—clinical, non-clinical, and quality—would be incredibly helpful.

5. With reference to lines 480 to 491, is it clear from the guidance what the eligibility criteria for notifiable trials are?

- Yes
- No

6. With reference to lines 480 to 491, are there any specific situations in which it would be unclear whether or not a trial is considered notifiable?

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- Yes
- No

If so, please describe these scenarios, providing as much detail as possible (optional):

Having the two tables as inclusion and exclusion, with 'yes' having different meanings, is not helpful and is confusing. It is recommended to have a single table where 'yes' means eligible and 'no' means not, with the crosses for the 'exclusion' criteria in the 'no' column.

For the eligibility criterion regarding a previous trial being approved, clarification is required as to whether a sponsor is expected to check public databases. For example, is a non-commercial sponsor expected to check or be aware of commercial submissions that meet the criterion? If not, it should be clear that this applies to prior approvals from the same sponsor. A similar point applies to the awareness of safety concerns: What are the expectations for how a sponsor checks for safety issues? The guidance should outline what is required (also to enable appropriate documentation in the event of a later GCP inspection).

7. With reference to lines 492 to 531, is the guidance clear on how to apply for clinical trial approval of a notifiable trial (including what happens if the licensing authority objects to the notification)?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

Line 503 states that additional information 'may' be requested – at what time point? If this is asked for, how will this impact the assessment timeline? Indeed, this information should be provided as part of the initial application documentation and checked as part of validation.

For the table in lines 489 and 504, what exactly is meant by 'the same or equivalent particulars and documents'? For example, does the protocol/IB/IMPD need to have the same version number? This aspect needs to be much more evident in terms of what the expectations are.

Line 517 – extra 'be' in the sentence.

Line 524 – if a notification application is ineligible and a full assessment is done, it should be clear whether the clock restarts or the time already elapsed is considered.

Line 531—If the licensing authority contacts the sponsor to inform them of a full assessment, it should clarify whether this is done within 14 days or not.

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8. With reference to the table (lines 588 to 599), are there any examples of modifications that are missing from the table?

- Yes
- No

If so, please provide these examples (optional):

The acceptability of the "Use of new measurements for the primary endpoint" as a B is contingent on the condition that these new measures do not expose participants to greater risk or inconvenience (e.g., an additional ultrasound is acceptable, but a liver biopsy is not).

The classification of 'Changes to the design of the trial which have a significant impact on statistical consideration' as a B may be appropriate. However, while the guidance clarifies that an increase in sample size is classified as an A, additional guidance is needed to determine if such changes affect exposure to the IMP (e.g., new randomisation ratios). This guidance should specify whether these considerations apply universally or should depend on the expected level of risk.

Lastly, the table still refers to 'amendment' in the first example. Many modifications may involve multiple changes spanning several categories. It would be helpful to clarify that if any changes meet the Route A criteria, Route A must be followed, even if Route B changes are also included.

9. With reference to lines 600 to 662 and 716 to 783, is the guidance clear on how to apply for approval to make a Route A substantial modification (including where the trial was not approved through combined review)?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

It is presumed the first process outlined is for Route A, as Route B modification has automatic approval from the MHRA and, therefore, is not subject to a request for further information (line 631). The flowchart in line 661 indicates it is for Route A, but the main text does not. Therefore, line 623 needs to clarify Route A.

Line 688 – same comment as for initial application notifications, in that it states ‘may be requested. Surely the information must be submitted with the main documentation?

Line 736 – missing ‘are’

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10. With reference to the table (lines 588 to 593), can you think of any specific modifications where you are unclear whether or not it would be considered a Route B substantial modification?

- Yes
- No

If so, please describe these modifications, providing as much detail as possible (optional):

See Q8 response.

11. With reference to lines 663 to 715, is the guidance clear on how to apply for approval to make a Route B substantial modification (including what happens if the licensing authority objects to a notification?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

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12. Is there any information missing that would help your understanding of the process of applying to modify a clinical trial approval?

- Yes
- No

If so, please describe this information (optional):

13. With reference to lines 817 to 845, is the guidance clear on how to report a suspected unexpected serious adverse reaction to the licensing authority?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

14. With reference to lines 855 to 940, is it clear what should be included in a DSUR?

- Yes

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- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

15. With reference to lines 913 to 937, please describe any other example approaches to preparing a DSUR that it would be useful to include.

A trial being conducted by a non-commercial sponsor but using an IMP being developed by a large pharmaceutical (pharma) company and who is therefore responsible for the DSUR submission.

16. With reference to lines 941 to 972, is it clear how to submit a DSUR to the licensing authority?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

17. With reference to lines 973 to 1028, is the guidance clear on how to notify an urgent safety measure (USM) to the licensing authority?

- Yes
- No

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If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

Line 979 states 24 hours. Will MHRA operate a 24/7 phone line or an out-of-hours daily service at set times or should this be one working day?

18. Is there any information missing that would help your understanding of the safety reporting processes?

- Yes
- No

If so, please describe this information (optional):

See response to Q17

19. With reference to lines 1052 to 1082, is the guidance clear on when and how to submit an end of trial notification?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible (optional):

There is a reference to local end-of-trial declarations, but there is no further information on how this can be done if a sponsor wishes.

20. Is the transition guidance clear?

- Yes
- No

If no, please identify where the guidance is not clear, referencing section titles and line numbers where possible:

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Understanding the transition rules is entirely dependent on the dates referred to, so it cannot be reviewed in full until dates are included. It is presumed there will be a cut-off date for the new legislation to become applicable, and then it is not really a transition period; it is all-or-nothing for initial applications with no choice on the sponsors' behalf (as there was in the EU). However, this could be clarified on the MHRA website. But it requires a bit of careful reading to be understood. Simplify, mainly to be clear, that the new rules apply to the entire study once a new rule substantial amendment is submitted.

21. Are there any scenarios not covered by the transition guidance?

- Yes
- No

If so, please describe these scenarios, providing as much detail as possible:

Where more than one study with the same IMP is being conducted, it is clear that old rules studies will have new PV rules applied, resulting in some old and new rules running simultaneously. These mixed rules approach may be confusing. It should be clarified whether this is the intended approach or if new rules should apply to the entire development programme—either from the approval of a new rules trial, after a set date (e.g., one year to allow ongoing studies to conclude), or from the filing of the first transitional DSUR.

Further clarification is needed on how this process will function.