

# Chapter 7: Clinical Investigation / Performance Studies

## Section 31 - Clinical evaluation (general medical devices)

### Background

31.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) require that, prior to obtaining a UKCA marking and placing a device on the Great Britain market, manufacturers must ensure that the design and manufacture of a device does not compromise the clinical condition of patients and users.

31.2 To do this a manufacturer must systematically collect, analyse and assess the clinical data relevant to the medical device in order to verify the safety and performance of that device - this is known as a **clinical evaluation**. Clinical data is safety and/or clinical performance information that is generated from the use of a medical device in humans. A number of data sources can be used, including data from an equivalent device, literature reviews and data obtained through the monitoring of medical devices once they are on the market.

31.3 However, sometimes there are gaps in the clinical data that cannot be addressed by other means. Where there is not sufficient pre-existing evidence to demonstrate that the device conforms with the relevant safety and performance requirements, the manufacturer should carry out a **clinical investigation** to:

- verify that under normal conditions of use the performance characteristics of the device are those intended by the manufacturer, and
- determine any undesirable side-effects and to assess whether these are acceptable risks when weighed against the intended performance of the device.

31.4 If such an investigation is necessary, the manufacturer must make an application to the MHRA before the investigation is due to begin. The clinical investigation may only then proceed provided no grounds for objection are raised by the MHRA within the statutory review time constraint. The MHRA will reach a decision, aided by a number of expert assessors.

31.5 The MHRA considers that it is best practice for clinical investigations to have a sponsor, who must take responsibility for the initiation, management and financing of the clinical investigation. The sponsor can be the manufacturer or another entity, such as a health institution.

31.6 We also consider it best practice for clinical investigations to have a principal clinical investigator, who is responsible for the conduct of a clinical investigation and takes responsibility for the health and safety of the subjects involved.

- 31.7 Sponsors and investigators are responsible for ensuring that the investigation is conducted in full accordance with the approved clinical investigation plan (CIP) and the requirements of the UK medical devices regulations. Deviations from the CIP must be reported to the MHRA and there must be adequate monitoring in place to ensure that the rights, safety and wellbeing of subjects are protected.
- 31.8 The clinical evaluation, including data collected through the clinical investigation, is assessed by an Approved Body, in cases where oversight from an Approved Body is required, during the conformity assessment process (see Chapter 6).
- 31.9 The UK medical devices regulations could include more detailed requirements for how a clinical evaluation must be conducted and documented by the medical device manufacturer. The objective of this would be to ensure that medical device manufacturers conduct effective clinical evaluations of their medical devices in a consistent and systematic way, taking into account all relevant clinical data, in order to demonstrate that a medical device is safe and performs as intended. This would help ensure that medical devices are not placed on the UK market unless there is sufficient evidence of their safety and performance.

### **Possible Changes and Questions**

- 31.10 The MHRA has identified that, in line with the objectives outlined above, the UK medical devices regulations could be amended to provide additional detail on the content and scope of a clinical evaluation, as well as the processes for conducting and documenting a clinical evaluation. Specific proposals are outlined in this section. Please note that additional questions, covering transitional arrangements for clinical investigations, are set out in Chapter 15.

### **Equivalent devices**

- 31.11 Currently, manufacturers can use the clinical data arising from investigations of a similar “equivalent” device as evidence that their own device is safe and performs as intended (due to the similarities between the devices). Manufacturers often claim equivalence on the basis that ‘part’ of a device is similar to another device. For example, a manufacturer may claim equivalence to a device that has the same function or dimensions even if it is made from different materials. This can result in ‘product creep’ where new devices on the market in practice become very different from their ‘equivalent’ devices. The MHRA considers that the UK medical devices regulations could introduce stricter requirements for claiming equivalence to prevent this from occurring. Such requirements could include:
- a. an equivalent medical device must be “entirely equivalent” to the manufacturer’s medical device (on a biological, physical, and clinical basis). This would mean that the manufacturer would not be able to claim equivalence to a part of that medical device; equivalence could only be claimed in relation to the whole device

- b. where a manufacturer claims equivalence to a medical device which is not the manufacturer's medical device (i.e. it has been marketed by another manufacturer) they would be required to:
  - i. have a contract in place with that manufacturer to allow them full access to the technical documentation for the medical device on an ongoing basis, and
  - ii. ensure that the clinical evaluation of the medical device they are claiming equivalence to meets the UK medical devices regulations and, where relevant, demonstrate this to their Approved Body, and
  - iii. have post-market studies in place to collect their own data for their medical device - which would need to be validated, where relevant, by an Approved Body (i.e. except where the medical device is a Class I device).
- c. manufacturers of certain medical devices e.g. implantable and Class III medical devices must, in their clinical evaluation for the device, include data from their own clinical investigations unless:
  - i. the medical device has been designed by minor modifications of an entirely equivalent medical device with a sufficient clinical evaluation, already marketed by the same manufacturer (the MHRA would provide guidance as to what constitutes a minor modification)
  - ii. the medical device is on an exempt list of medical devices and the clinical evaluation is based on sufficient clinical data
  - iii. In the above cases the manufacturer would still be required to have post-market studies in place to collect their own data for the medical device and this would need to be validated by an Approved Body.

**Q31.1 Do you think that the specific requirements, outlined in paragraph 31.11, that relate to claiming equivalence should be introduced? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q31.2 Please provide any additional information (for example outline what requirements you think should be introduced around claiming equivalence or explain why you do not agree that additional requirements should be introduced).**

### **Products without an intended medical purpose**

31.12 The MHRA considers that the UK medical devices regulations could be amended to require that clinical investigations or other pre-market studies involving human subjects / participants are performed for products without an intended medical purpose (see Chapter 1, Section 2), and that we propose to regulate such products under the UK medical devices regulations, unless reliance on existing clinical data from an entirely equivalent medical device is duly justified. This would bring a number of products without an intended medical purpose, such as non-prescription coloured contact lenses, or dermal fillers without a stated medical purpose into scope of these requirements, with the aim of delivering improved public and patient safety.

**Q31.3 Do you think that manufacturers of products without an intended medical purpose should be required to perform clinical**

**investigations or other pre-market studies involving human subjects / participants as set out in paragraph 31.12? ('Yes' / 'No' / 'Don't Know/No Opinion')**

Section 32 - Performance evaluation (IVDs)

**Background**

32.1 Manufacturers of *in vitro* diagnostic medical devices (IVDs) are not required to perform clinical evaluations. Instead they must conduct performance evaluations of their IVDs to ensure that they meet the essential requirements of the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations). This is because, while IVDs must be able to provide accurate medical information on individuals, the final clinical outcome for the patient is dependent on further diagnostic and/or therapeutic interventions. The data gathered through performance evaluation are used to build the clinical evidence for the IVD, i.e., the proof that the IVD is safe and achieves the intended clinical benefit.

32.2 As part of the performance evaluation, the manufacturer must systematically collect, analyse and assess the data relevant to the IVD in order to establish or verify the performance of the IVD.

32.3 This performance evaluation is assessed by the Approved Body, where required, during the conformity assessment for the IVD.

32.4 Under the UK medical devices regulations, manufacturers of IVDs must provide adequate performance evaluation data as evidence of the performance of the IVD claimed by the manufacturer. No further requirements regarding performance evaluation are currently included under the UK regulations.

32.5 The UK medical devices regulations could include more detailed requirements for how a performance evaluation must be conducted and documented by the medical device manufacturer. The objective of this would be to ensure that medical device manufacturers conduct effective performance evaluations of their IVDs in a consistent and systematic way, which takes into account all the relevant data, in order to demonstrate that an IVD performs as intended. This would help ensure that IVDs are not placed on the UK market unless there is sufficient evidence of their safety and performance.

**Possible Changes and Questions**

**Clinical, scientific and analytical data requirements**

32.6 The MHRA considers that the UK medical devices regulations could be amended to explicitly require in legislation that conformity of an IVD with the UK medical devices regulations is based on conformance with the essential requirements. The

Regulations could, in particular, explicitly require evidence of scientific validity, and analytical and clinical performance data that provide sufficient clinical evidence. Manufacturers could be required to document this data in a performance evaluation report, to be included as part of the technical documentation for the device.

**Q32.1 Do you think that confirmation of conformity of an IVD with the UK medical devices regulations should be based on scientific validity, analytical and clinical performance data? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q32.2 Do you think that manufacturers should be required to produce a performance evaluation report as part of the technical documentation for the device? ('Yes' / 'No' / 'Don't Know/No Opinion')**

### **Performance evaluation requirements**

32.7 The MHRA has identified that the UK medical devices regulations could be amended to provide additional requirements for IVD manufacturers conducting performance evaluations. This could include more detailed requirements for the scope and content of a performance evaluation, including how a manufacturer must demonstrate the scientific validity and the analytical and clinical performance of the IVD. It could also include more detailed requirements regarding how the manufacturer should demonstrate that they have sufficient clinical evidence (data which shows the medical device is safe and performs as intended) and how a performance evaluation should be documented. These issues are explored in more detail below.

### **Clinical evidence requirements**

32.8 Currently, as set out above, IVD manufacturers must provide performance evaluation data to show that the device is safe and performs as intended. Data gathered through an IVD performance evaluation, in addition to other clinical data, contributes to the clinical evidence for an IVD. The UK medical devices regulations do not currently refer specifically to clinical evidence requirements.

32.9 The MHRA considers that the UK medical devices regulations could be amended to outline clinical evidence requirements. For example, the Regulations could require manufacturers to specify and justify the level of the clinical evidence necessary to demonstrate that the device is safe and performs as intended. Manufacturers could be required to include in their clinical evidence for an IVD, evidence from their own clinical performance studies (studies undertaken to confirm the analytical or clinical performance of a medical device) unless they can justify reliance on other sources of clinical performance data.

32.10 In addition, manufacturers could be required to continue to update the clinical evidence throughout the lifecycle of the device, for example, through ongoing monitoring of scientific developments and changes in medical practice. This would be

a new regulatory requirement. Please note that additional questions, covering transitional arrangements for performance studies, are set out in Chapter 15.

**Q32.3 Do you think manufacturers should be required to specify and justify the level of clinical evidence necessary to demonstrate conformity with the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q32.4 Do you think the UK medical devices regulations should require manufacturers to rely on data from their own clinical performance studies unless they can justify reliance on other sources of clinical performance data? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q32.5 If you have answered 'yes' to question 32.4, please outline what factors you think this justification could include.**

32.11 The UK medical devices regulations do not currently set out post-market requirements in relation to IVD performance evaluations. The MHRA considers that the Regulations could be amended to require that manufacturers update the clinical evidence for a medical device throughout the lifetime of that device. Manufacturers could also be required to update other technical documentation relating to their IVD with performance evaluation data. In particular, manufacturers could be required to:

- update the summary of safety and clinical performance (SSCP) (a mechanism for collating information on the medical device's safety, clinical data, and clinical performance (see Chapter 7, Section 47), and
- update the post-market performance follow-up report (PMPF) (a continuous process that updates the performance evaluation specifically addressed in the manufacturer's post-market surveillance plan) (see Chapter 8).

**Q32.6 Do you think the UK medical devices regulations should require that the performance evaluation is updated throughout the lifetime of the IVD and used to update the technical documentation listed in paragraph 32.11? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q32.7 If you have answered 'yes' to question 32.6, please outline how you think the performance evaluation should be updated by the manufacturer and if there is any other technical documentation which should be updated.**

**Q32.8 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 32.1-32.7, including any impacts on you or other stakeholder groups.**

## Section 33 - General requirements regarding clinical investigations (general medical devices)

### Background

- 33.1 A clinical investigation is any systematic investigation involving one or more human subject(s), undertaken to assess the safety and performance of a medical device.
- 33.2 Currently, manufacturers are, in certain circumstances, required to carry out a clinical investigation to demonstrate that their medical device complies with the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations).
- 33.3 All clinical investigations need a sponsor who must take responsibility for the initiation, management and financing the clinical investigation.
- 33.4 The UK medical devices regulations currently set out limited requirements for clinical investigations. These requirements could be updated to include additional detail and clarity so that clinical investigations are carried out appropriately and in a consistent manner. The objective would be to more effectively safeguard the health and welfare of clinical investigation participants and ensure that appropriate clinical data is obtained for a device in order to draw accurate, evidence-based conclusions about its safety and/or performance.

### Possible Changes and Questions

#### Requirements for clinical investigations

- 33.5 The MHRA considers that the UK medical devices regulations could be amended to set out that clinical investigations conducted for one or more of the following purposes shall be designed, authorised, conducted, recorded and reported in accordance with the UK medical devices regulations:
- a) to establish and verify that, under normal conditions of use the medical device achieves the performance intended by its manufacturer
  - b) to establish and verify the clinical benefits of a medical device as specified by its manufacturer
  - c) to establish and verify the clinical safety of the medical device and to determine any undesirable side-effects, under normal conditions of use of the medical device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the medical device.

**Q33.1 Do you think that clinical investigations regulated under the UK medical devices regulations should be limited to those carried out for one of the purposes outlined in paragraph 33.5? ('Yes' / 'No' / 'Don't Know/No Opinion')**

## **Requirement for non-UK clinical investigation and performance study sponsors to appoint a UK-based legal representative**

33.6 The MHRA considers that the UK medical device regulations could be amended to require that, where the sponsor of a clinical investigation is not established in the UK, that sponsor shall ensure that a person is established in the UK as its legal representative. This requirement could also be made in relation to non-UK-based sponsors of IVD performance studies. The UK medical devices regulations could require that this legal representative is responsible for ensuring compliance with the sponsor's obligations and acts as the addressee for all communications with the sponsor. The UK medical devices regulations could provide that any communication with that legal representative shall be deemed to be a communication with the sponsor.

**Q33.2 Do you think that, if the sponsor is based outside the UK, they should be required to appoint a legal representative in the UK as outlined in paragraph 33.6? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.3 Do you think that the legal representative should be responsible for ensuring compliance with the sponsor's obligations and be the addressee for all communications with the sponsor? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.4 Do you think that any communication with that legal representative should be deemed to be communication with the sponsor? ('Yes' / 'No' / 'Don't Know/No Opinion')**

## **Sponsor obligations**

33.7 The MHRA considers that the UK medical devices regulations could be amended to set out the obligations applicable to the sponsor of a clinical investigation. This could include requirements for the sponsor to:

- a. provide and make publicly available a summary of the study, at the time of submitting a formal clinical investigation application to the MHRA and at the time of notifying the MHRA when a clinical investigation has come to an end
- b. keep technical documentation available for the MHRA for a specified time period after the clinical investigation has been carried out – including where the sponsor goes bankrupt or ceases activity prior to this period. The UK medical devices regulations currently require that the technical documentation is kept available for a minimum period of five years. We are proposing to increase this to a minimum period of 10 years after the last device was placed on the market for most devices and 15 years for implantable devices
- c. ensure that, in addition to the current requirement under the UK medical devices regulations to report any serious adverse events to the MHRA, the following are also reported in a timely manner:

- i. any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation
- ii. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
- d. appoint a monitor that is independent from the investigational site to ensure that the clinical investigation is conducted in accordance with the clinical investigation plan (CIP), the principles of good clinical practice and the UK medical devices regulations
- e. provide evidence that the investigation is being conducted in line with good clinical practice, for instance through internal or external inspection
- f. prepare a clinical investigation report.

**Q33.5 Do you think the UK medical devices regulations should set out the obligations of the sponsor, including those outlined in paragraph 33.7? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.6 Please outline any other requirements which should be introduced for the sponsor.**

### **Clinical investigation report**

33.8 The UK medical devices regulations require that a written report of a clinical investigation must be produced. This must contain a critical evaluation of all the data collected during the clinical investigation. The MHRA considers that the UK medical devices regulations could be amended to specifically require sponsors to prepare and publish a clinical investigation report and could set out the minimum requirements for the report. This would help ensure a more consistent and comprehensive approach to compiling clinical investigation reports. These requirements could include, for example:

- a. title of the investigation, details of the investigational device and details of the author
- b. a summary of the investigation - covering purpose, investigational design, methods used, results and conclusion
- c. the completion date of the investigation, and any details of early termination, temporary halts or suspensions of investigations
- d. investigational device description and intended purpose
- e. a summary of the clinical investigation plan - covering objectives, design, ethical aspects, monitoring and quality measures, selection criteria, target patient populations, sample size, treatment schedules, follow-up duration, concomitant treatments and statistical plan
- f. results of the clinical investigation covering, with rationale and justification, subject demographics, analysis of results, details of subgroup analysis
- g. summary of serious adverse events, adverse device effects, device deficiencies and any relevant corrective actions
- h. discussion and overall conclusions covering safety and performance results and assessment of risks and clinical benefits.

33.9 The UK medical devices regulations could be amended to require the sponsor to publish a publicly accessible version of the clinical investigation report. The objective

would be to improve public and patient safety through increased transparency. If we were to introduce this requirement, we would take account of data protection obligations and commercially confidentiality considerations.

**Q33.7 Do you think the UK medical devices regulations should set out the minimum requirements for the clinical investigation report, including those outlined in paragraph 33.8? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.8 Please outline any other requirements which should be introduced for the clinical investigation report.**

**Q33.9 Do you think the UK medical devices regulations should require the sponsor to publish the clinical investigation report? ('Yes' / 'No' / 'Don't Know/No Opinion')**

### **Requirements for conducting clinical investigations**

33.10 The UK medical devices regulations currently include requirements regarding the objectives, methods and ethical considerations for a clinical investigation. The Regulations could be amended to further clarify and supplement the existing requirements - for example, that:

- a. as part of the study's investigational design, a list of the technical and functional features of the device and the related expected clinical outcomes shall be provided
- b. the endpoints of the clinical investigation shall address the intended purpose, and clinical benefits
- c. the endpoints shall be determined and assessed using scientifically valid methodologies – and the primary endpoint shall be appropriate to the device and clinically relevant
- d. personnel involved in the conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational device and good clinical practice. This training shall be verified and where necessary arranged by the sponsor and documented appropriately
- e. the clinical investigation report must include any negative findings.

**Q33.10 Do you think the UK medical devices regulations should include the additional detailed requirements relating to the methods for a clinical investigation as outlined in paragraph 33.10? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.11 Please outline any other requirements which should be introduced relating to the methods for a clinical investigation.**

## Clinical investigation plan

33.11 The UK medical devices regulations currently require that clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device.

33.12 The MHRA considers that the Regulations could be amended to set out more detailed requirements regarding what must be included in the clinical investigation plan (CIP), to help ensure a consistent and comprehensive approach. This could include requirements for the CIP to set out the rationale, objectives, design methodology, monitoring, conduct, record keeping and the method of analysis for the clinical investigation. Specific requirements could be for the CIP to include, for example:

- a. details of the sponsor and, where applicable, the sponsor's legal representative established in the UK, the principal investigator at each investigational site and the coordinating investigator for the investigation.
- b. a brief description of how the clinical investigation is financed and of the agreement between the sponsor and the site
- c. an overall synopsis of the clinical investigation
- d. identification and description of the device, including its intended purpose, manufacturer and traceability, the target population and materials coming into contact with the human body
- e. risks and clinical benefits of the device to be examined
- f. objectives and hypotheses of the clinical investigation
- g. design of the clinical investigation with evidence of its scientific robustness and validity
- h. information on subjects, including selection criteria, size of investigation population and representativeness of investigation population in relation to target population
- i. details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors
- j. a monitoring plan, including data management and accountability for the device
- k. description of the Informed consent process
- l. safety reporting, including definitions of adverse events and serious adverse events, device deficiencies, procedures and timelines for reporting.

**Q33.12 Do you think the UK medical devices regulations should set out the detailed requirements for the clinical investigation plan, including those outlined in paragraph 33.12? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.13 Please outline any other requirements should be introduced for the clinical investigation plan.**

## Conditions that must be met when performing a clinical investigation

33.13 The UK medical devices regulations currently set out the conditions that must be met when performing a clinical investigation. For example, the Regulations provide that the clinical investigation is subject to authorisation by the MHRA and that an ethics committee must have issued a favourable opinion in relation to the investigation. The MHRA considers that these conditions could be expanded to specifically include, for example:

- a. the sponsor, or its legal representative or a contact person pursuant to paragraph 33.6, is established in the UK (as set out in paragraph 33.6)
- b. vulnerable populations and subjects are appropriately protected
- c. certain populations, such as pregnant or breastfeeding women, are not excluded from a clinical investigation unless adequately justified
- d. the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences - and compliance with this condition is constantly monitored
- e. the subject or, where the subject is not able to give informed consent, his or her legally designated representative has given informed consent in accordance with Section 35
- f. the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with the contact details of an entity where further information can be received in case of need
- g. the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with relevant data protection legislation are safeguarded
- h. the medical care provided to the subjects is the responsibility of a licensed medical practitioner or registered healthcare practitioner to provide the relevant patient care under clinical investigation conditions
- i. no undue influence, including that of a financial nature, is exerted on the subject, or, where applicable, on his or her legally designated representatives, to participate in the clinical investigation
- j. the enhanced requirements for the clinical investigation application, report and plan (as outlined in section 38) are fulfilled
- k. the enhanced sponsor obligations are fulfilled (as outlined in paragraph 33.7).

**Q33.14 Do you think the UK medical devices regulations should set out the requirements that must be met for performing a clinical investigation, including those outlined in paragraph 33.13? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.15 Please outline any other requirements that should be met when performing a clinical evaluation.**

## **Rights of participants to withdraw from a clinical investigation**

33.14 The UK medical devices regulations do not currently address the rights of subjects / participants to withdraw from clinical investigations. The MHRA considers that the Regulations could be amended to provide that a subject/participant has the right to withdraw from a clinical investigation at any time without any resulting detriment and without having to provide any justification.

**Q33.16 Do you think the UK medical devices regulations should set out the rights of subjects/participants to withdraw from clinical investigations, as outlined in paragraph 33.14? ('Yes' / 'No' / 'Don't Know/No Opinion')**

## **Requirements for the investigator and other personnel**

33.15 The UK medical devices regulations currently provide that clinical investigations must be performed under the responsibility of a medical practitioner or another authorised qualified person. The MHRA considers that the Regulations could be amended to, in addition, set out requirements for the investigator (the individual responsible for the conduct of a clinical investigation at a clinical investigation site) of a clinical investigation and the personnel involved in the clinical investigation. This could include, for example, that the investigator shall be a person exercising a profession requiring the necessary scientific knowledge and experience in patient care, and that other personnel should be suitably qualified by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.

**Q33.17 Do you think the qualification requirements for investigators of clinical investigations and personnel involved in clinical investigations, including those outlined in paragraph 33.15, should be introduced? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q33.18 Please outline any other requirements which should be introduced for investigators of clinical investigations and the personnel involved in clinical investigations.**

## **Section 34 - General requirements regarding performance studies (IVDs)**

### **Background**

34.1 A performance study is a study undertaken to establish or confirm the analytical or clinical performance of an IVD.

34.2 Manufacturers may be required to carry out a performance study to demonstrate that their *in vitro* diagnostic medical device (IVD) complies with the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations).

34.3 The UK medical devices regulations include limited requirements for performance studies on IVDs. Additional requirements could be introduced to ensure that performance studies are carried out in a consistent way, that appropriate data is obtained and that the health and welfare of participants (where applicable) is protected.

## Possible Changes and Questions

### Requirements for all performance studies

34.4 The UK medical devices regulations do not currently set any requirements regarding the circumstances and conditions of use in which a performance study should be carried out. The MHRA considers that the Regulations could be amended to provide that, where appropriate, performance studies should be performed in circumstances similar to the normal conditions of use of the medical device. Possible exemptions from this requirement could include, for example, self-test IVDs in cases where it is necessary to conduct the performance study in a clinical setting or cases where invasive samples are required, and the performance study can be conducted on left-over lab samples.

**Q34.1 Do you think we should require that, where appropriate, performance studies be performed in circumstances similar to the normal conditions of use of the medical device? ('Yes' / 'No' / 'Don't Know/No Opinion')**

### Additional requirements for certain performance studies

34.5 The UK medical devices regulations could detail additional specific requirements that would apply to any performance study:

- in which surgically invasive sample-taking is done only for the purpose of the performance study
- that is an interventional clinical performance study (a study in which the test results are intended to be used in patient management or treatment), or
- where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies.

These performance studies could be required to meet the requirements of this Section as well as other Sections in this Chapter (Chapter 7) relating to performance studies.

**Q34.2 Do you think the UK medical devices regulations should set out in detail the specific requirements for the performance studies in paragraph 34.5 above? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.3 If you have answered 'yes' to question 34.2, please outline what you think the specific requirements of the performance study should be.**

## **Sponsor obligations**

34.6 The UK medical devices regulations require that an IVD manufacturer or their UK Responsible Person draw up a statement that includes data allowing the identification of the device in question, an evaluation plan, the list of laboratories or other institutions participating in the evaluation study, information about study timings and participants and confirmation that the device conforms with the requirements of the Regulations other than aspects covered by the evaluation.

34.7 The MHRA considers that, for clarity, the UK medical devices regulations could be amended to set out, in addition, specific obligations for the sponsor of a performance study. This could include obligations to:

- a. report a summary of the study outcome to MHRA
- b. provide a publicly accessible summary of the study, at the time of registration and upon completion of the study
- c. keep technical documentation available for the MHRA for a specified time period after the performance study has been carried out – including where the sponsor goes bankrupt or ceases activity prior to this period. This documentation must currently be kept for a period ending at least five years after the end of the performance evaluation. We are considering extending this to 10 years after the last device has been placed on the market
- d. have an agreement in place to ensure that any serious adverse events or any medical device deficiency that might have led to a serious adverse event are reported by the investigator or investigators to the sponsor in a timely manner
- e. appoint a monitor that is independent from the investigational site to ensure that the clinical performance study is conducted in accordance with the clinical performance study plan (CPSP), the principles of good clinical practice and the UK medical devices regulations
- f. complete the follow-up of investigation subjects and devices involved in the performance study.

**Q34.4 Do you think the UK medical devices regulations should set out the obligations for the sponsor of a performance study, including those outlined in paragraph 34.7? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.5 Please outline any other obligations for the sponsor of a performance study which should be.**

## Clinical performance study plan

34.8 The UK medical devices regulations require that manufacturers or their UK Responsible Persons draw up a statement setting out key details regarding the clinical performance study. The MHRA considers that the Regulations could be amended to require that sponsors implement a clinical performance study plan (CPSP) which sets out the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping for the clinical performance study and to clarify that this obligation also extends to performance studies other than clinical performance studies (for example analytical performance studies).

**Q34.6 Do you think sponsors should be required to implement a clinical performance study plan? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.7 Do you think detailed requirements for the clinical performance study plan should be set out in the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.8 If you have answered 'yes' to question 34.7, please outline what you think the requirements for the clinical performance study plan should be.**

**Q34.9 Do you think this obligation should also extend to other types of performance studies (other than clinical performance studies)? ('Yes' / 'No' / 'Don't Know/No Opinion')**

## Detailed requirements for performance studies

34.9 The UK medical devices regulations require that an evaluation plan for a performance study is drawn up stating, in particular the purpose, scientific, technical or medical grounds, scope of the evaluation and the number of devices concerned. The MHRA considers that the Regulations could be amended to outline the detailed requirements for the purpose, methods, objectives and ethical considerations for a performance study. This could include setting out the information that must be covered in the clinical performance study plan (CPSP), which could include:

- The CPSP shall define the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical performance study. It shall contain, in particular, the following information:
  - (a) identification and description of the device, its intended purpose(s) (including the target condition, function, population, user and setting) the analyte(s) (constituent of a sample with a measurable property (ISO 18113-1)) and / or measurand(s) (quantity intended to be measured (JCGM 200:2012)) and their scientific validity, the metrological traceability, and the manufacturer
  - (b) information about the type of specimens under investigation including how the specimen is taken, stored and transported and by whom

- (c) overall synopsis of the clinical performance study, its design type, such as observational, interventional, the objectives and hypotheses of the study, reference to the current state of the art in diagnosis and/or medicine
- (d) a description of the expected risks and benefits of the device and of the clinical performance study in the context of the state of the art in clinical practice, and with the exception of studies using left-over samples, the medical procedures involved and patient management
- (e) the instructions for use of the device or test protocol, the necessary training and experience of the user, the appropriate calibration procedures and means of control, the indication of any other devices, medical devices, medicinal product or other articles to be included or excluded and the specifications on any comparator or comparative method used as reference
- (f) description of and justification for the design of the clinical performance study, its scientific robustness and validity, including the statistical design, power and analysis plan and details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors
- (g) the analytical performance including consideration of trueness (bias), precision (repeatability, intermediate-imprecision and reproducibility), analytical sensitivity, linearity, limits of detection and quantification, measuring-range, analytical specificity (cross-reactivity, endogenous and exogenous interference and matrix effects) and appropriate criteria for specimen collection and handling, where appropriate
- (h) parameters of clinical performance to be determined for each intended purpose, and with the exception of studies using left-over samples the specified clinical outcomes/endpoints (primary/secondary) used with a justification and the potential implications for individual health and/or public health management decisions
- (i) information on the performance study population: specifications of the subjects, selection criteria, size of performance study population, prevalence of the target condition, representativity of target population and, if applicable, information on vulnerable subjects involved, such as children, pregnant women, immuno-compromised or elderly subjects
- (j) information on the performance study setting and IVD users and representativity of the intended use.
- (k) information on use of data out of left over specimens banks, genetic or tissue banks, patient or disease registries etc. with description of reliability and representativity and statistical analysis approach; description of specimen collection, handling and storage conditions; assurance of relevant method for determining the true clinical status of patient specimens.

**Q34.10 Do you think the UK medical devices regulations should set detailed requirements for the purpose, methods, objectives and ethical considerations for a performance study including those outlined in paragraph 34.9? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.11 Please outline any other requirements for performance studies which should be introduced.**

**Clinical performance study report**

34.10 The MHRA considers that the UK medical devices regulations could be amended to require sponsors to prepare and publish a clinical performance study report, containing documented information on the clinical performance study plan and results and conclusions of the clinical performance study, including negative findings. The UK medical devices regulations could clarify that this obligation also extends to other types of performance studies (such as analytical performance studies).

**Q34.12 Do you think sponsors should be required to provide a clinical performance study report? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.13 Do you think the UK medical devices regulations should set out the minimum requirements for the clinical performance study report? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.14 If you have answered 'yes' to question 34.13, please outline what the requirements for the clinical performance study report should be.**

**Q34.15 Do you think this obligation should also extend to analytical performance studies? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.16 If you have answered 'yes' to question 34.15, what types of performance study (other than clinical performance studies) do you think should be subject to a clinical performance study report?**

**Q34.17 Do you think the UK medical devices regulations should require the clinical performance study report be published? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Ethical review**

34.11 Performance studies that involve the use of human samples are in some circumstances subject to ethical review. The ethical review is performed by an ethics committee either before or in parallel with notification to the MHRA. The MHRA considers that the manufacturer should be required to submit a copy of the research ethics committee approval to the MHRA.

34.12 However, in certain circumstances – for example, when de-identified surplus samples are used by laboratories for assay validation and verification, a review by an ethics committee is not required. The MHRA considers that the UK medical devices

regulations could be amended to clarify that any performance study involving human samples must be subject to a review by an ethics committee.

**Q34.18 Do you think the UK medical devices regulations should require ALL performance studies involving human samples to be subject to ethical review by an ethics committee? ('Yes' / 'No' / 'Don't Know/No Opinion')**

### **Performance studies involving companion diagnostics**

- 34.13 A companion diagnostic is a device which is essential for the safe and effective use of a corresponding medicinal product to:
- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product, or
  - identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

- 34.14 The MHRA considers that the UK medical devices regulations could be amended to require that performance studies involving companion diagnostics are subject to the same requirements as all other performance studies. The UK medical devices regulations could provide that this requirement does not apply to performance studies involving companion diagnostics using only left-over samples. Such studies would however need to be notified to the MHRA.

**Q34.19 Do you think that performance studies involving companion diagnostics should be subject to the same requirements as all other performance studies? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.20 Do you think that performance studies involving companion diagnostics using only left-over samples should NOT be subject to the same requirements as all other performance studies? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.21 Do you think that performance studies involving companion diagnostics using only left-over samples should be notified to the MHRA? ('Yes' / 'No' / 'Don't Know/No Opinion')**

### **Performance study conditions**

- 34.15 The MHRA considers that the UK medical devices regulations could be amended to set out the conditions that should be met when conducting a performance study as referred to in Section 34 above. Such conditions could include that:
- the performance study is the subject of an authorisation by the MHRA
  - an ethics committee has issued a favourable opinion; in relation to the performance study

- c. the sponsor, or its legal representative is established in the UK
- d. vulnerable populations and subjects are appropriately protected
- e. certain populations, such as pregnant or breastfeeding women, are not excluded from a performance study unless adequately justified
- f. the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored
- g. the subject or, where the subject is not able to give informed consent in line with relevant data protection legislation, his or her legally designated representative has given informed consent in accordance with Section 35
- h. the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with the contact details of an entity where further information can be received in case of need
- i. the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with relevant data protection legislation are safeguarded
- j. the performance study has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the performance study plan and constantly monitored
- k. the medical care provided to the subjects is the responsibility of a licensed medical practitioner or registered healthcare practitioner, who must provide the relevant patient care under clinical investigation conditions
- l. no undue influence, including that of a financial nature, is exerted on the subject, or, where applicable, on his or her legally designated representatives, to participate in the performance study
- m. where appropriate, biological safety testing reflecting the latest scientific knowledge or any other test deemed necessary in the light of the medical device's intended purpose has been conducted
- n. in the case of clinical performance studies, the analytical performance has been demonstrated, taking into consideration the state of the art
- o. in the case of interventional clinical performance studies, the analytical performance and scientific validity has been demonstrated, taking into consideration the state of the art. Where, for companion diagnostics, the scientific validity is not established, the scientific rationale for the use of the biomarker shall be provided
- p. the technical safety of the medical device with regard to its use has been proven, taking into consideration the state of the art as well as provisions in the field of occupational safety and accident prevention.

**Q34.22 Do you think the conditions for conducting a performance study should be set out in the UK medical devices regulations, including those outlined in paragraph 34.15? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.23 Please outline any other conditions which should be met when conducting a performance study.**

## **Rights of participants to withdraw from a performance study**

34.16 The UK medical devices regulations do not currently address the rights of subjects / participants to withdraw from performance studies. The MHRA considers that the Regulations could be amended to provide that a subject / participant has the right to withdraw from a performance study at any time without any resulting detriment and without having to provide any justification. This would provide clarity to study subjects / participants so that they are aware of and able to exercise their rights.

**Q34.24 Do you think the rights of subjects to withdraw from a performance study should be included in the UK medical devices regulations, as set out in paragraph 34.16? ('Yes' / 'No' / 'Don't Know/No Opinion')**

## **Requirements for the investigator and other personnel**

34.17 The UK medical devices regulations do not currently set any qualification requirements for the key personnel involved in conducting a performance study. The MHRA considers that the Regulations could be amended to set out requirements for the investigator (the individual responsible for the conduct of a performance study at a performance study site) of a performance study and the personnel involved in the study. This could include, for example, that the investigator shall be a person exercising a profession requiring the necessary scientific knowledge and experience in patient care or laboratory medicine, and that other personnel should be suitably qualified by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.

**Q34.25 Do you think the UK medical devices regulations should set out requirements for the investigator and other personnel involved in the performance study, including those outlined in paragraph 34.17? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.26 If you have answered 'yes' to question 34.25, please outline what you think the requirements should be.**

## **Settings, facilities and users for conducting performance studies**

34.18 The UK medical devices regulations do not currently set any requirements regarding the facilities pertaining to performance studies. There are currently no requirements, for example, regarding the appropriateness or fitness for purpose of the facility in which the study is conducted (for example, in terms of the laboratory, equipment and expertise of study personnel).

34.19 Similarly, the UK medical devices regulations do not currently set requirements for the appropriateness of the study's setting and users to the intended setting in which the IVD will be used and intended user population.

34.20 The MHRA considers that the UK medical devices regulations could be amended to require that, where appropriate, the settings and facilities in which a performance study is to be conducted are similar to the settings and facilities where the medical device is intended to be used. In addition, the Regulations could require that, where appropriate, the study's users are representative of the intended users (e.g. self-testing, near patient and laboratory professional use, healthcare professionals) of the IVD subject to the performance study. For example, if the medical device is intended to be used as a self-test in a home setting, the performance study should mirror this.

**Q34.27 Do you think that the UK medical devices regulations should require that, where appropriate, the facilities where the performance study is to be conducted should be suitable for the conduct of the study? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.28 Do you think that, where appropriate, the setting and users of the medical device in the clinical performance study should be similar to the intended setting and intended users of the medical device? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q34.29 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 34.1-34.28, including any impacts on you or other stakeholder groups.**

## Section 35 - Informed consent

### Background

35.1 'Informed consent' means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation or performance study, after having been informed of all aspects of the clinical investigation or performance study that are relevant to their participation. In the case of minors and of incapacitated subjects, an authorisation or agreement can be provided from their legally designated representative to include them in the clinical investigation or performance study.

35.2 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not include any specific requirements for obtaining informed consent from individuals participating in clinical investigations or performance studies.

35.3 Setting this out in the UK medical devices regulations would ensure that persons conducting clinical investigations or clinical performance studies could effectively obtain informed consent from and provide greater protection to participants – particularly those from vulnerable groups.

## Possible Changes and Questions

35.4 The MHRA considers that the UK medical devices regulations could be amended to include detailed requirements for obtaining informed consent from individuals participating in a clinical investigation or performance study.

**Q35.1 Do you think the UK medical devices regulations should include requirements for obtaining informed consent from individuals participating in a clinical investigation or performance study? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q35.2 If you have answered 'yes' to question 35.1, please outline what the requirements for obtaining informed consent should be.**

**Q35.3 Please outline any circumstances in which you think the requirements for obtaining informed consent might be waived? (e.g. observational studies where only fully de-identified data and/or left-over samples are used, or cluster randomised trials).**

**Q35.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 35.1-35.3, including any impacts on you or other stakeholder groups.**

## Section 36 - Specific requirements for clinical investigations / performance studies

### Background

36.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not include any specific requirements for clinical investigations or performance studies which are performed on vulnerable subjects / participants, including minors and pregnant or breastfeeding women.

36.2 Setting requirements for vulnerable subjects / participants in the UK medical devices regulations would ensure that persons conducting clinical investigations or clinical performance studies are informed of special measures that must be taken when such groups are involved, thus safeguarding the health and welfare of participants within these groups.

## Possible Changes and Questions

### Additional requirements regarding minors

36.3 The MHRA considers that the UK medical devices regulations could include additional requirements for clinical investigations or performance studies on minors. For example, the Regulations could require that:

- a. the informed consent of the minor's legally designated representative has been obtained
- b. the minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity
- c. the clinical investigation or performance study either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors
- d. there are scientific grounds for expecting that participation in the performance study will produce a direct benefit to the minor subject outweighing the risks and burdens involved.

**Q36.1 Do you think additional requirements, including those outlined in paragraph 36.3, should be required for clinical investigations or performance studies on minors? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q36.2 Please outline any other requirements which should be introduced for clinical investigations or performance studies on minors.**

### Additional requirements regarding pregnant or breastfeeding women

36.4 The MHRA considers that the UK medical devices regulations could include additional requirements for clinical investigations or performance studies on pregnant or breastfeeding women. For example, the Regulations could require that:

- a. the clinical investigation or performance study has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved
- b. where a direct benefit is not expected, a study of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding - and the clinical investigation or performance study poses a minimal risk to the subject concerned, her embryo, foetus or child after birth
- c. a study on pregnant or breastfeeding women has been specifically designed to generate clinical data on this patient group
- d. where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child

**Q36.3 Do you think additional requirements, including those outlined in paragraph 36.4, should be required for clinical investigations or**

**performance studies on pregnant or breastfeeding women? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q36.4 Please outline any other requirements which should be introduced for clinical investigations or performance studies on pregnant or breastfeeding women.**

**Q36.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 36.1-36.4, including any impacts on you or other stakeholder groups.**

## Section 37 - Clinical investigations / Performance studies in emergency situations

### **Background**

37.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not include any specific requirements for clinical investigations or performance studies in emergency situations.

37.2 Making provision for emergency situations in the UK medical devices regulations would ensure that persons conducting clinical investigations or clinical performance studies are aware of the procedures they would need to follow in order that all appropriate measures have been taken to safeguard participant health and welfare in an emergency situation.

### **Possible Changes and Questions**

#### **Informed consent in emergency situations**

37.3 The MHRA considers that the UK medical devices regulations could be amended to set out the conditions in which informed consent to participate in a clinical investigation or performance study may be obtained, and information on the clinical investigation or performance study may be given, after the decision to include the subject / participant in a clinical investigation or performance study due to an emergency situation. This could apply, for example, in cases where the patient's condition is life-threatening.

**Q37.1 Do you think the conditions should be set out in which informed consent to participate in a clinical investigation or performance study may be obtained or given after the decision to include the subject in a clinical investigation or performance study due to an emergency situation? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q37.2 Please provide your reasoning (including any available relevant evidence) to support your answer to question 37.1, including any impacts on you or other stakeholder groups.**

### **Compensation requirements**

37.4 The UK medical devices regulations require that insurance of subjects / participants is in place with regards to clinical investigations. No such requirement is currently made for performance studies. The MHRA considers that the UK medical devices regulations could be amended to require sponsors to put in place systems for compensation for any damage suffered by a subject as a result of participating in a clinical investigation or performance study conducted in Great Britain. This could be in the form of insurance, a guarantee or a similar arrangement, proportionate to the nature and extent of the risk.

**Q37.3 Do you think that systems should be put in place for compensation as set out in paragraph 37.4? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q37.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 37.1-37.3, including any impacts on you or other stakeholder groups.**

## Section 38 - Application for clinical investigations / performance studies

### **Background**

38.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) set out some requirements relating to applications to the MHRA for a clinical investigation. However, the relevant procedures for application by the sponsor and response from the MHRA and the associated timescales could be more detailed to ensure that the procedure is clear and runs smoothly, and that appropriate expectations are set to increase fairness and transparency.

### **Possible Changes and Questions**

#### **Application form and accompanying documentation**

38.2 The MHRA considers that the UK medical devices regulations could be amended to outline detailed requirements for the clinical investigation or performance study application form and the accompanying documentations required. For example, the Regulations could specify that the application will collect information on:

- a. the status of the clinical investigation, such as. the first submission, resubmission, amendment

- b. details and/or reference to and summary of the clinical evaluation plan or performance study plan
- c. brief description of the device, its classification and other information necessary for the identification of the device and device type
- d. if applicable, information regarding a comparator device, its classification and other information necessary for the identification of the comparator device
- e. details of the anticipated start date and duration of the investigation.

**Q38.1 Do you think detailed requirements for the clinical investigation or performance study application form and the accompanying documentation required, including those outlined in paragraph 38.2 should be outlined? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q38.2 Please outline any other requirements which should be introduced for the application form and accompanying documentation.**

### **Application timescales**

38.3 The MHRA considers that UK medical devices regulations could be amended to outline the relevant timescales that the applicant and the MHRA should conform to when an application for a clinical investigation or performance study is submitted to the MHRA. One option would be to retain the current 60 days for assessment but to also include timescales for validation. This could, for example, comprise 10 days for the MHRA to respond to the initial submission, 10 days for the sponsor to provide additional information, and a further five days for MHRA to review whether the submission is valid.

**Q38.3 Do you think the UK medical devices regulations should outline the relevant timescales that the applicant and the MHRA should conform to when an application for a clinical investigation or performance study is submitted to the MHRA? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q38.4 If you have answered 'yes' to question 38.3, please outline what appropriate timescale should be.**

**Q38.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 38.1-38.4, including any impacts on you or other stakeholder groups.**

## Section 39 - Assessment of applications for clinical investigation / performance study by the MHRA

### Background

39.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not require the MHRA to assess applications for performance studies. Neither do they set out how an application for a clinical investigation must be assessed by the MHRA. This is currently provided for in guidance. The UK medical devices regulations could require that performance study applications are assessed by the MHRA. The Regulations could also set detailed requirements for the assessment of clinical investigation and performance study applications for purpose of aiding transparency.

### Possible Changes and Questions

#### Assessment of clinical investigation and performance study applications

39.2 The MHRA considers that the UK medical devices regulations could require the MHRA to assess applications for performance studies.

**Q39.1 Do you think the MHRA should be required to assess applications for performance studies? ('Yes' / 'No' / 'Don't Know/No Opinion')**

39.3 The MHRA considers that the UK medical devices regulations could be amended to set out the detailed requirements for assessment of the application for a clinical investigation or performance study by the MHRA. This could include:

- a. requiring that any person responsible for validating and assessing the application, or deciding on it has relevant qualifications and experience and is independent of the sponsor, the investigator and anyone involved in financing the investigation or study
- b. that the design of the clinical investigation or performance study should be examined by the MHRA to ensure that potential remaining risks to subjects or third persons, after risk minimisation, are justified, when weighed against the clinical benefits to be expected
- c. the circumstances in which the MHRA could refuse the authorisation of a clinical investigation or performance study.

**Q39.2 Do you think the detailed requirements for assessment of the application for clinical investigations or performance study should be outlined by the MHRA? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q39.3 If you have answered 'yes' to question 39.2, please outline what you think the requirements for assessment of the application for clinical investigation or performance study should be.**

**Q39.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 39.1-39.3, including any impacts on you or other stakeholder groups.**

## Section 40 - Conduct of a clinical investigation / performance study

### **Background**

40.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not include detailed requirements for the conduct of a clinical investigation or performance study. Setting these requirements out in further detail would ensure that clinical investigations and performance studies are conducted appropriately to safeguard the health and welfare of participants.

### **Possible Changes and Questions**

#### **Procedures for conducting clinical investigations and performance studies**

40.2 The MHRA considers that the UK medical devices regulations could be amended to require sponsors and investigators to:

- a. have adequate processes in place to identify deviations from the clinical investigation plan, and record and report any such deviations immediately
- b. have established a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the medical devices used in the investigation.

**Q40.1 Do you think the UK medical devices regulations should set out the requirements for the conduct of a clinical investigation or performance study, as outlined in paragraph 40.2? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q40.2 Please outline any other requirements which should be introduced for the conduct of a clinical investigation or performance study.**

#### **Inspection of study sites**

40.3 The MHRA considers that the UK medical devices regulations could be amended to require the MHRA to inspect, at an appropriate level, clinical investigation or performance study site(s) to check that clinical investigations and performance

studies are conducted in accordance with the UK medical devices regulations and the investigation plan. Performance studies involving self-test devices or clinical investigations of a medical device conducted in a home setting could be exempted from this requirement.

**Q40.3 Do you think that the MHRA should be required to inspect, at an appropriate level, clinical investigation, or performance study site(s)? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q40.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 40.1-40.3, including any impacts on you or other stakeholder groups.**

Section 41 - Clinical investigations / Performance studies regarding devices bearing the UKCA marking

### **Background**

41.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not include a requirement for sponsors to notify the MHRA in cases where a clinical investigation or performance study is to be conducted to further assess a device which is already UKCA marked according to its intended purpose.

41.2 Including such a requirement would give the MHRA greater oversight of post-market clinical follow-up (PMCF) and post-market performance follow-up (PMPF) studies (see Chapter 8) being conducted on these devices.

### **Possible Changes and Questions**

#### **Notifications to the MHRA**

41.3 The MHRA considers that the UK medical devices regulations could be amended to set out that, where a clinical investigation or performance study is to be conducted to further assess, within the scope of its intended purpose, a UKCA marked device in accordance with Chapter 8 ('PMCF investigation') / ('PMPF study'), and where the investigation or study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome, the sponsor shall notify the MHRA within a specified time period prior to the start of the study.

**Q41.1 Do you think the sponsor should be required to notify the MHRA of a clinical investigation or performance study within a specified time period prior to the start of that clinical investigation**

or performance study as outlined in paragraph 41.3? ('Yes' / 'No' / 'Don't Know/No Opinion')

**Q41.2** If you have answered 'yes' to question 41.1, please outline what you think the specified time period should be.

**Q41.3** Please provide your reasoning (including any available relevant evidence) to support your answers to questions 41.1-41.2, including any impacts on you or other stakeholder groups.

## Section 42 - Modifications to clinical investigations / performance studies

### Background

42.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not set out detailed requirements that must be met when there is a modification to a clinical investigation or performance study.

### Possible Changes and Questions

#### Procedures relating to modifications to a clinical investigation or performance study

42.2 The MHRA considers that the UK medical devices regulations could be amended to set out the procedures that should be followed in cases where a sponsor intends to introduce modifications to a clinical investigation or performance study that are likely to have an impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation/study. These procedures could include, for example:

- a. the requirement to notify the MHRA, within a specified time period, of the reasons for and the nature of those modifications and to include an updated version of the relevant documentation as part of the notification
- b. the sponsor may implement the modifications within a specified time frame after they have notified the MHRA, providing that the MHRA has not notified the sponsor of a refusal and that they have received a favourable opinion from an ethics committee – the MHRA may extend this time period for the purpose of consulting with experts.

**Q42.1** Do you think the UK medical devices regulations should set out the procedures for sponsors intending to introduce modifications to a clinical investigation or performance study, including the procedures outlined in paragraph 42.2? ('Yes' / 'No' / 'Don't Know/No Opinion')

**Q42.2 Please outline any other procedures which should be introduced and/or what the timeframes for the procedures in paragraph 42.2/suggested procedures should be.**

**Q42.3 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 42.1-42.2, including any impacts on you or other stakeholder groups.**

Section 43 - Corrective measures to be taken by the MHRA in relation to a clinical investigation / performance study

### **Background**

43.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) could be amended to specify in legislation, the corrective measures that could be taken by the MHRA in regards to a clinical investigation or performance study.

### **Possible Changes and Questions**

#### **Corrective measures**

43.2 The MHRA considers that the UK medical devices regulations could be amended to provide that, where the MHRA has grounds for considering that the requirements set out in the UK medical devices regulations in regards to a performance study are not met, it may take at least any of the following measures:

- a. revoke the authorisation for the performance study
- b. suspend or terminate the performance study
- c. require the sponsor to modify any aspect of the performance study.

**Q43.1 Do you think that the MHRA should be able to take the measures outlined in paragraph 43.2 in cases where it is considered that the requirements of the UK medical devices regulations in regards to a performance study have not been met? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q43.2 Please outline any other measures which should be introduced for either a clinical investigation or performance study.**

#### **Engagement with the sponsor or investigator**

43.3 Before taking any of the measures outlined in paragraph 43.2 (suggested measures for both clinical investigations and performance studies), the MHRA could be required, except where immediate action is required, to ask the sponsor or the

investigator or both for their opinion and require that this is given within a specified time period.

**Q43.3 Do you think, except where immediate action is required, that the sponsor or the investigator or both should be asked for their opinion regarding the corrective measures outlined in paragraph 43.2 (suggested measures)? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q43.4 If you have answered 'yes' to question 43.3, please outline what you think should be the specified time period for the sponsor or investigator to give their opinion.**

**Q43.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 43.1-43.4, including any impacts on you or other stakeholder groups.**

Section 44 - Information from the sponsor at the end of a clinical investigation / performance study or in the event of a temporary halt or early termination

### **Background**

44.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) do not set out detailed requirements for the information that the sponsor must provide at the end of a clinical investigation or performance study or in the event of a temporary halt or early termination.

### **Possible Changes and Questions**

#### **Applicable procedures in the event of a temporary halt or early termination**

44.2 The UK medical devices regulations require that the manufacturer or their UK Responsible Person must notify the MHRA at the end of the clinical investigation and provide justification in cases where premature termination has resulted. The MHRA considers that the Regulations could be amended to extend this requirement to performance studies and set out the procedures that must be undertaken and the timeframes that would apply when making such a notification at the end of a clinical investigation or performance study or in the event of a temporary halt or early termination. This could include:

- a. requiring the sponsor of the clinical investigation to notify the MHRA within a specified time period of the end of the study
- b. requiring the sponsor to notify MHRA, within a specified time period of the end of / early termination of a performance study

- c. requiring the sponsor, within a specified time period of the end of / early termination of a clinical investigation or performance study, to submit a clinical investigation or performance study report

**Q44.1 Do you think the procedures, including those outlined in paragraph 44.2 which must be undertaken and the timeframes which would apply at the end of a clinical investigation or performance study, or in the event of a temporary halt or early termination should be specified? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q44.2 Please outline any other procedures which should be included and/or what the timeframe for notification should be for the procedures in paragraph 44.2/suggested procedures.**

**Q44.3 Please provide your views on what these timescales should be and your reasoning (including any available relevant evidence) to support your answers to questions in 44.1-44.2, including any impacts on you or other stakeholder groups.**

## Section 45 - Recording and reporting of adverse events that occur during clinical investigations / performance studies

### **Background**

45.1 The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) include a requirement that all serious adverse events relating to clinical investigations must be fully recorded and immediately notified to the MHRA. The detailed requirements and processes for serious adverse event reporting are provided for in guidance. There is currently no requirement to report serious adverse events relating to IVD performance evaluations to the MHRA.

45.2 The MHRA considers that these additional details could be set out in the UK medical devices regulations with regards to both clinical investigations and performance studies, to ensure timely and accurate reporting of adverse events which occur during clinical investigations or performance studies.

### **Possible Changes and Questions**

45.3 The MHRA considers that the UK medical devices regulations could be amended to require the sponsor to fully record, for both clinical investigations and performance studies, all of the following:

- a. any adverse event of a type identified in the clinical investigation or performance study plan as being critical to the evaluation of the results of that clinical investigation or performance study
- b. any serious adverse event
- c. any medical device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
- d. any new findings in relation to any event referred to in points (a) to (c).

The Regulations could require that, upon request by the MHRA, the sponsor shall provide the information in points (a) to (d).

**Q45.1 Do you think sponsors of clinical investigations and performance studies should be required in legislation to fully record and provide information on adverse events, serious adverse events and medical device deficiencies including those set out in points (a) to (d) in paragraph 45.3? ('Yes' / 'No' / 'Don't Know/No Opinion')**

45.4 The MHRA considers that the UK medical devices regulations could be amended to require sponsors to report, for both clinical investigations and performance studies, without delay to the MHRA, all of the following:

- a. any serious adverse event
- b. any medical device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
- c. any new findings in relation to any event referred to in points (a) and (b).

45.5 The period for reporting should take account of the severity of the event. The Regulations could provide that, where necessary, the sponsor may submit an initial report that is incomplete followed up by a complete report.

**Q45.2 Do you think sponsors should be required to report, without delay, to the MHRA, the events set out in points (a) to (c) of paragraph 45.4? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q45.3 Do you think, where necessary, sponsors should be able to submit an initial report that is incomplete, followed up by a complete report? ('Yes' / 'No' / 'Don't Know/No Opinion')**

45.6 The MHRA considers that the UK medical devices regulations could be amended to require sponsors to report to the MHRA any event referred to in paragraph 45.4 that has occurred in a country outside the UK in which a clinical investigation or performance study is performed under the same clinical investigation or performance study plan. This would provide a more comprehensive evidence base for the medical device / IVD in question.

**Q45.4 Do you think the UK medical devices regulations should require sponsors to report to the MHRA any event referred to in**

paragraph 45.4 that has occurred in a non-UK country in which a clinical investigation or performance study is performed under the same clinical investigation or performance study plan? ('Yes' / 'No' / 'Don't Know/No Opinion')

**Q45.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 45.1-45.4, including any impacts on you or other stakeholder groups.**

## Section 46 - Types of clinical investigations / performance studies and exemptions / authorisations

### **Background**

- 46.1 The requirements under the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) can, in some cases, create barriers for certain organisations, such as academic institutions, that may wish to carry out certain types of clinical investigation or performance study. This in turn could potentially prevent new devices coming to market, thus reducing the availability of different types of device on the UK market and hindering innovation.
- 46.2 The MHRA considers that, in specific circumstances, exemptions to certain requirements of the UK medical devices regulations could be put in place. This could apply, for example, in relation to smaller early feasibility clinical investigations or to performance studies carried out by academic institutions that will be followed up with further studies, where there is no involvement from industry.
- 46.3 Health institutions that manufacture devices for use in house and that do not intend to place such devices on the market are currently exempt from the UK medical devices regulations (please see Chapter 3, Section 8 for further information on and possible amendments to the health institution exemption). The MHRA considers this type of exemption may not be appropriate in certain circumstances - for example, in cases where a large number of patients are involved in a pivotal clinical investigation or performance study, or where the investigation or study results would be particularly significant.

### **Possible Changes and Questions**

- 46.4 The MHRA considers that the UK medical devices regulations could be amended to include exemptions from some of the requirements of the UK medical devices regulations for certain clinical investigations and performance studies. This could apply, for example, in cases where an academic institute is working with a health institution to conduct a proof of concept or early feasibility study (limited clinical investigation of a device early in development, typically used to evaluate the device

design concept with respect to initial clinical safety) on a medical device without any input from industry, and there is no intention to place the device on the market. However, all studies would still need to be registered with the MHRA before taking place.

**Q46.1 Do you think the UK medical devices regulations should allow for exemptions from some of the requirements of the Regulations for certain types of clinical investigations and performance studies as outlined in paragraph 46.4? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q46.2 If you have answered 'yes' to question 46.1 please outline what types of clinical investigations and performance studies you think should be exempted.**

46.5 Please see Chapter 3, Section 8 for further information on exemptions for health institutions from certain requirements of the UK medical devices regulations. The MHRA considers that the Regulations could be amended to ensure that certain types of clinical investigation and performance study conducted by health institutions must be notified to the MHRA for authorisation before proceeding. This could include, for example, larger pivotal or confirmatory clinical investigation studies which are conducted to provide the information necessary to evaluate the clinical performance, effectiveness or safety of the investigational device.

**Q46.3 Do you think that healthcare institutions should be required to notify certain types of clinical investigation / performance studies to the MHRA for authorisation before proceeding? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q46.4 If you have answered 'yes' to question 46.3 please outline what types of clinical investigations / performance studies should meet the requirements of the UK medical devices regulations.**

**Q46.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 46.1-46.4, including any impacts on you or other stakeholder groups.**

## Section 47 - Summary of safety and clinical performance

### Background

47.1 There is currently no requirement for manufacturers of medical devices to make clinical data publicly available for medical devices placed on the Great Britain market.

47.2 We could introduce a requirement for manufacturers of certain medical devices to publish data on device safety and performance following UKCA marking, for intended users of the medical device.

47.3 This could provide users and potential users of a medical device, including patients and clinicians, with a means of obtaining accessible and easy to understand information about a medical device, thus enhancing transparency and enabling clinicians and patients/users to make more informed decisions about medical devices.

47.4 This information could be captured in the form of a 'summary of safety and clinical performance (SSCP)' which could include information on the medical device's safety, clinical data, and clinical performance.

## **Possible Changes and Questions**

### **Minimum requirements for the SSCP**

47.5 The MHRA considers that the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) could be amended to set out the minimum requirements for what should be included in the SSCP. Such requirements could include:

- a. the identification of the medical device and the manufacturer, including the Basic UDI-DI and, if already issued, the MHRA identifying number for registration
- b. the intended purpose of the medical device and any indications, contra-indications and target populations
- c. a description of the medical device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other medical devices and products, which are intended to be used in combination with the medical device
- d. possible diagnostic or therapeutic alternatives
- e. the metrological traceability of assigned values
- f. reference to any designated standards applied
- g. the summary of clinical evaluation (see Section 31), and relevant information on post-market clinical follow-up (see Chapter 8)
- h. the summary of the clinical investigation/performance evaluation, and relevant information on the post-market clinical follow-up
- i. suggested profile and training for users
- j. information on any residual risks and any undesirable effects, warnings and precautions including disclosing potential allergenic ingredients
- k. summary of the Approved Body conformity assessment.

47.6 The UK medical devices regulations could be amended to require medical device manufacturers to produce an SSCP, written in plain English, for certain types of medical devices. Such medical devices could include:

- a. Class III medical devices (excluding investigational medical devices)
- b. Implantable medical devices (excluding investigational medical devices)
- c. High to medium risk IVDs i.e. those that would be classed as List A and List B under the UK medical devices regulations (excluding custom-made medical devices and medical devices for performance study).

**Q47.1 Do you think the UK medical devices regulations should introduce the requirement for an SSCP for medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q47.2 If you have answered 'yes' to question 47.1, please outline what classes/types of medical devices should require an SSCP.**

**Q47.3 Do you think the UK medical devices regulations should set out the minimum content of the SSCP included in paragraph 47.5? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q47.4 Please outline any other content which should be included in the SSCP for a medical device.**

47.7 As expanded on in Chapter 4, Section 20, the UK medical devices regulations could be amended to require manufacturers to upload the full SSCP or a link to the SSCP (hosted externally) to the MHRA registration system.

**Q47.5 Please select one of the following:**

- a. the manufacturer should upload the full SSCP to the MHRA registration system
- b. the manufacturer should upload a link to the SSCP to the registration system
- c. the manufacturer should not be required to upload the SSCP to the registration system
- d. other – please specify
- e. don't know/no opinion

47.8 The UK medical devices regulations could be amended to require Approved Bodies to validate the SSCP. This could work in the following way:

- a. the medical device manufacturer to submit the draft of the SSCP to the Approved Body involved in the conformity assessment of the medical device
- b. the Approved Body to validate the SSCP
- c. the medical device manufacturer to upload the validated SSCP to the MHRA registration system (where a draft SSCP has initially been uploaded)

**Q47.6 Do you think an Approved Body should validate the SSCP for a medical device? ('Yes' / 'No' / 'Don't Know/No Opinion')**

**Q47.7 If you have answered 'yes' to question 47.6, please outline how this procedure should be carried out.**

**Q47.8 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 47.1-47.7, including any impacts on you or other stakeholder groups.**

To share your views on requiring SSCPs as part of the requested registration information and timeframes for this please see Chapter 4, Section 20.