A N N E X E S

ANNEX XV

CLINICAL INVESTIGATIONS

CHAPTER I

GENERAL REQUIREMENTS

1. Ethical principles

Each step in the clinical investigation, from the initial consideration of the need for and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles.

2. Methods

2.1. Clinical investigations shall 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 regarding the safety, performance and aspects relating to benefit-risk of devices as referred to in Article 62(1); the clinical investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions. The rationale for the design and chosen statistical methodology shall be presented as further described in Section 3.6 of Chapter II of this Annex.

2.2. The procedures used to perform the clinical investigation shall be appropriate to the device under investigation.

2.3. The research methodologies used to perform the clinical investigation shall be appropriate to the device under investigation.

2.4. Clinical investigations shall be performed in accordance with the clinical investigation plan by a sufficient number of intended users and in a clinical environment that is representative of the intended normal conditions of use of the device in the target patient population. Clinical investigations shall be in line with the clinical evaluation plan as referred to in Part A of Annex XIV.

2.5. All the appropriate technical and functional features of the device, in particular those involving safety and performance, and their expected clinical outcomes shall be appropriately addressed in the investigational design. A list of the technical and functional features of the device and the related expected clinical outcomes shall be provided.

2.6. The endpoints of the clinical investigation shall address the intended purpose, clinical benefits, performance and safety of the device. The endpoints shall be determined and assessed using scientifically valid methodologies. The primary endpoint shall be appropriate to the device and clinically relevant.

2.7. Investigators shall have access to the technical and clinical data regarding the device. Personnel involved in the conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational device, and as regards the clinical investigation plan and good clinical practice. This training shall be verified and where necessary arranged by the sponsor and documented appropriately.

2.8. The clinical investigation report, signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings.

CHAPTER II

DOCUMENTATION REGARDING THE APPLICATION FOR CLINICAL INVESTIGATION

For investigational devices covered by Article 62, the sponsor shall draw up and submit the application in accordance with Article 70 accompanied by the following documents:

1. Application form

The application form shall be duly filled in, containing information regarding:

1.1. name, address and contact details of the sponsor and, if applicable, name, address and contact details of its contact person or legal representative in accordance with Article 62(2) established in the Union;

1.2. if different from those in Section 1.1, name, address and contact details of the manufacturer of the device intended for clinical investigation and, if applicable, of its authorised representative;

1.3. title of the clinical investigation;

1.4. status of the clinical investigation application (i.e. first submission, resubmission, significant amendment);

1.5. details and/or reference to the clinical evaluation plan;

1.6. If the application is a resubmission with regard to a device for which an application has been already submitted, the date or dates and reference number or numbers of the earlier application or in the case of significant amendment, reference to the original application. The sponsor shall identify all of the changes from the previous application together with a rationale for those changes, in particular, whether any changes have been made to address conclusions of previous competent authority or ethics committee reviews;

1.7. if the application is submitted in parallel with an application for a clinical trial in accordance with Regulation (EU) No 536/2014, reference to the official registration number of the clinical trial;

1.8. identification of the Member States and third countries in which the clinical investigation is to be conducted as part of a multicentre or multinational study at the time of application;

1.9. a brief description of the investigational device, its classification and other information necessary for the identification of the device and device type;

1.10. information as to whether the device incorporates a medicinal substance, including a human blood or plasma derivative or whether it is manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives;

1.11. summary of the clinical investigation plan including the objective or objectives of the clinical investigation, the number and gender of subjects, criteria for subject selection, whether there are subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation;

1.12. if applicable, information regarding a comparator device, its classification and other information necessary for the identification of the comparator device;

1.13. evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the clinical investigation plan;

1.14. details of the anticipated start date and duration of the investigation;

1.15. details to identify the notified body, if already involved at the stage of application for a clinical investigation;

1.16. confirmation that the sponsor is aware that the competent authority may contact the ethics committee that is assessing or has assessed the application; and

1.17. the statement referred to in Section 4.1.

2. Investigator's Brochure

The investigator's brochure (IB) shall contain the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application. Any updates to the IB or other relevant information that is newly available shall be brought to the attention of the investigators in a timely manner. The IB shall be clearly identified and contain in particular the following information:

2.1. Identification and description of the device, including information on the intended purpose, the risk classification and applicable classification rule pursuant to Annex VIII, design and manufacturing of the device and reference to previous and similar generations of the device.

2.2. Manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use, including storage and handling requirements, as well as, to the extent that such information is available, information to be placed on the label, and instructions for use to be provided with the device when placed on the market. In addition, information relating to any relevant training required.

2.3. Pre-clinical evaluation based on relevant pre-clinical testing and experimental data, in particular regarding in-design calculations, *in vitro* tests, *ex vivo* tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable.

2.4. Existing clinical data, in particular:

— from relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the device and/or of equivalent or similar devices;

— other relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices of the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety-related issues and any corrective actions taken.

2.5. **[**[X1]Summary of the benefit-risk analysis and the risk management, including information regarding known or foreseeable risks, any undesirable side-effects, contraindications and warnings.**]**

2.6. In the case of devices that incorporate a medicinal substance, including a human blood or plasma derivative or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives, detailed information on the medicinal substance or on the tissues, cells or their derivatives, and on the compliance with the relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives, as well as evidence for the added value of incorporation of such constituents in relation to the clinical benefit and/or safety of the device.

2.7. A list detailing the fulfilment of the relevant general safety and performance requirements set out in Annex I, including the standards and CS applied, in full or in part, as well as a description of the solutions for fulfilling the relevant general safety and performance requirements, in so far as those standards and CS have not or have only been partly fulfilled or are lacking.

2.8. A detailed description of the clinical procedures and diagnostic tests used in the course of the clinical investigation and in particular information on any deviation from normal clinical practice.

Editorial Information

X1 Substituted by Corrigendum to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Official Journal of the European Union L 117 of 5 May 2017).

3. Clinical Investigation Plan

The clinical investigation plan (CIP) shall set out the rationale, objectives, design methodology, monitoring, conduct, record-keeping and the method of analysis for the clinical investigation. It shall contain in particular the information as laid down in this Annex. If part of this information is submitted in a separate document, it shall be referenced in the CIP.

3.1. General

3.1.1. Single identification number of the clinical investigation, as referred to in Article 70(1).

3.1.2. Identification of the sponsor — name, address and contact details of the sponsor and, where applicable, the name, address and contact details of the sponsor's contact person or legal representative in accordance with Article 62(2) established in the Union.

3.1.3. Information on the principal investigator at each investigational site, the coordinating investigator for the investigation, the address details for each investigational site and the emergency contact details for the principal investigator at each site. The

roles, responsibilities and qualifications of the various kinds of investigators shall be specified in the CIP.

3.1.4. A brief description of how the clinical investigation is financed and a brief description of the agreement between the sponsor and the site.

3.1.5. Overall synopsis of the clinical investigation, in an official Union language determined by the Member State concerned.

3.2. Identification and description of the device, including its intended purpose, its manufacturer, its traceability, the target population, materials coming into contact with the human body, the medical or surgical procedures involved in its use and the necessary training and experience for its use, background literature review, the current state of the art in clinical care in the relevant field of application and the proposed benefits of the new device.

3.3. Risks and clinical benefits of the device to be examined, with justification of the corresponding expected clinical outcomes in the clinical investigation plan.

3.4. Description of the relevance of the clinical investigation in the context of the state of the art of clinical practice.

3.5. Objectives and hypotheses of the clinical investigation.

3.6. Design of the clinical investigation with evidence of its scientific robustness and validity.

3.6.1. General information such as type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan.

3.6.2. Information on the investigational device, on any comparator and on any other device or medication to be used in the clinical investigation.

3.6.3. Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or, elderly subjects.

3.6.4. Details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors.

3.6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice.

3.6.6. Monitoring plan.

3.7. Statistical considerations, with justification, including a power calculation for the sample size, if applicable.

3.8. Data management.

3.9. Information about any amendments to the CIP.

3.10. Policy regarding follow-up and management of any deviations from the CIP at the investigational site and clear prohibition of use of waivers from the CIP.

3.11. Accountability regarding the device, in particular control of access to the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices.

3.12. Statement of compliance with the recognised ethical principles for medical research involving humans, and the principles of good clinical practice in the field of clinical investigations of devices, as well as with the applicable regulatory requirements.

3.13. Description of the Informed consent process.

3.14. Safety reporting, including definitions of adverse events and serious adverse events, device deficiencies, procedures and timelines for reporting.

3.15. Criteria and procedures for follow-up of subjects following the end, temporary halt or early termination of an investigation, for follow-up of subjects who have withdrawn their consent and procedures for subjects lost to follow-up. Such procedures shall for implantable devices, cover as a minimum traceability.

3.16. A description of the arrangements for taking care of the subjects after their participation in the clinical investigation has ended, where such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

3.17. Policy as regards the establishment of the clinical investigation report and publication of results in accordance with the legal requirements and the ethical principles referred to in Section 1 of Chapter I.

3.18. List of the technical and functional features of the device, with specific mention of those covered by the investigation.

3.19. Bibliography.

4. Other information

4.1. A signed statement by the natural or legal person responsible for the manufacture of the investigational device that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.

4.2. Where applicable according to national law, copy of the opinion or opinions of the ethics committee or committees concerned. Where according to national law the opinion or opinions of the ethics committee or committees is not required at the time of the submission of the application, a copy of the opinion or opinions shall be submitted as soon as available.

4.3. Proof of insurance cover or indemnification of subjects in case of injury, pursuant to Article 69 and the corresponding national law.

4.4. Documents to be used to obtain informed consent, including the patient information sheet and the informed consent document.

4.5. Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data, in particular:

— organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

— a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and

— a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.

4.6. Full details of the available technical documentation, for example detailed risk analysis/management documentation or specific test reports, shall, upon request, be submitted to the competent authority reviewing an application.

CHAPTER III

OTHER OBLIGATIONS OF THE SPONSOR

1. The sponsor shall undertake to keep available for the competent national authorities any documentation necessary to provide evidence for the documentation referred to in Chapter II of this Annex. If the sponsor is not the natural or legal person responsible for the manufacture of the investigational device, that obligation may be fulfilled by that person on behalf of the sponsor.

2. The Sponsor shall have an agreement in place to ensure that any serious adverse events or any other event as referred to in Article 80(2) are reported by the investigator or investigators to the sponsor in a timely manner.

3. The documentation mentioned in this Annex shall be kept for a period of at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. In the case of implantable devices, the period shall be at least 15 years.

Each Member State shall require that this documentation is kept at the disposal of the competent authorities for the period referred to in the first subparagraph in case the sponsor, or its contact person or legal representative as referred to in Article 62(2) established within its territory, goes bankrupt or ceases its activity prior to the end of this period.

4. The Sponsor shall appoint a monitor that is independent from the investigational site to ensure that the investigation is conducted in accordance with the CIP, the principles of good clinical practice and this Regulation.

5. The Sponsor shall complete the follow-up of investigation subjects.

6. The Sponsor shall provide evidence that the investigation is being conducted in line with good clinical practice, for instance through internal or external inspection.

7. The Sponsor shall prepare a clinical investigation report which includes at least the following:

— Cover/introductory page or pages indicating the title of the investigation, the investigational device, the single identification number, the CIP number and the details with signatures of the coordinating investigators and the principal investigators from each investigational site.

— Details of the author and date of the report.

— A summary of the investigation covering the title, purpose of the investigation, description of the investigation, investigational design and methods used, the results of the investigation and conclusion of the investigation. The completion date of

the investigation, and in particular details of early termination, temporary halts or suspensions of investigations.

— Investigational device description, in particular clearly defined intended purpose.

— 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, statistical plan, including hypothesis, sample size calculation and analysis methods, as well as a justification.

— Results of the clinical investigation covering, with rationale and justification, subject demographics, analysis of results related to chosen endpoints, details of subgroup analysis, as well as compliance with the CIP, and covering follow-up of missing data and of patients withdrawing from the clinical investigation, or lost to follow-up.

— Summary of serious adverse events, adverse device effects, device deficiencies and any relevant corrective actions.

— Discussion and overall conclusions covering safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device, limitations of the investigation.

Status:
Point in time view as at 31/01/2020.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) 2017/745 of the European Parliament and of the Council, ANNEX XV.