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 (Text with EEA relevance)

CHAPTER VI

CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS

Article 61

Clinical evaluation

1 Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk-ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.

2 For all class III devices and for the class IIb devices referred to in point (b) of Article 54(1), the manufacturer may, prior to its clinical evaluation and/or investigation, consult an expert panel as referred to in Article 106, with the aim of reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigation. The manufacturer shall give due consideration to the views expressed by the expert panel. Such consideration shall be documented in the clinical evaluation report referred to in paragraph 12 of this Article.

The manufacturer may not invoke any rights to the views expressed by the expert panel with regard to any future conformity assessment procedure.

3 A clinical evaluation shall follow a defined and methodologically sound procedure based on the following:

a a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where the following conditions are satisfied:
   — it is demonstrated that the device subject to clinical evaluation for the intended purpose is equivalent to the device to which the data relate, in accordance with Section 3 of Annex XIV, and
   — the data adequately demonstrate compliance with the relevant general safety and performance requirements;

b a critical evaluation of the results of all available clinical investigations, taking duly into consideration whether the investigations were performed under Articles 62 to 80, any acts adopted pursuant to Article 81, and Annex XV; and

c a consideration of currently available alternative treatment options for that purpose, if any.

4 In the case of implantable devices and class III devices, clinical investigations shall be performed, except if:

— the device has been designed by modifications of a device already marketed by the same manufacturer,

— the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, in accordance with Section 3 of Annex XIV and this demonstration has been endorsed by the notified body, and

— the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

In this case, the notified body shall check that the PMCF plan is appropriate and includes post market studies to demonstrate the safety and performance of the device.

In addition, clinical investigations need not be performed in the cases referred to in paragraph 6.

5 A manufacturer of a device demonstrated to be equivalent to an already marketed device not manufactured by him, may also rely on paragraph 4 in order not to perform a clinical investigation provided that the following conditions are fulfilled in addition to what is required in that paragraph:

— the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis, and

— the original clinical evaluation has been performed in compliance with the requirements of this Regulation,

and the manufacturer of the second device provides clear evidence thereof to the notified body.

6 The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

a which have been lawfully placed on the market or put into service in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation:

— is based on sufficient clinical data, and

— is in compliance with the relevant product-specific CS for the clinical evaluation of that kind of device, where such a CS is available; or

b that are sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific CS, where such a CS is available.

7 Cases in which paragraph 4 is not applied by virtue of paragraph 6 shall be justified in the clinical evaluation report by the manufacturer and in the clinical evaluation assessment report by the notified body.

8 Where justified in view of well-established technologies, similar to those used in the exempted devices listed in point (b) of paragraph 6 of this Article, being used in other devices, or where justified in order to protect the health and safety of patients, users or other persons or other aspects of public health, the Commission is empowered to adopt delegated acts in accordance with Article 115 to amend the list of exempted devices referred to in the second subparagraph of

Article 52(4) and in point (b) of paragraph 6 of this Article, by adding other types of implantable or class III devices to that list or removing devices therefrom.

9 In the case of the products without an intended medical purpose listed in Annex XVI, the requirement to demonstrate a clinical benefit in accordance with this Chapter and Annexes XIV and XV shall be understood as a requirement to demonstrate the performance of the device. Clinical evaluations of those products shall be based on relevant data concerning safety, including data from post-market surveillance, PMCF, and, where applicable, specific clinical investigation. Clinical investigations shall be performed for those products unless reliance on existing clinical data from an analogous medical device is duly justified.

10 Without prejudice to paragraph 4, where the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performance intended and the claims of the manufacturer. In such a case, the manufacturer shall duly substantiate in the technical documentation referred to in Annex II why it considers a demonstration of conformity with general safety and performance requirements that is based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and pre-clinical evaluation, to be adequate.

11 The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with clinical data obtained from the implementation of the manufacturer's PMCF plan in accordance with Part B of Annex XIV and the post-market surveillance plan referred to in Article 84.

For class III devices and implantable devices, the PMCF evaluation report and, if indicated, the summary of safety and clinical performance referred to in Article 32 shall be updated at least annually with such data.

12 The clinical evaluation, its results and the clinical evidence derived from it shall be documented in a clinical evaluation report as referred to in Section 4 of Annex XIV, which, except for custom-made devices, shall be part of the technical documentation referred to in Annex II relating to the device concerned.

13 Where necessary to ensure the uniform application of Annex XIV, the Commission may, having due regard to technical and scientific progress, adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and of practical application. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 114(3).

Article 62

General requirements regarding clinical investigations conducted to demonstrate conformity of devices

1 Clinical investigations shall be designed, authorised, conducted, recorded and reported in accordance with the provisions of this Article and of Articles 63 to 80, the acts adopted pursuant to Article 81, and Annex XV, where carried out as part of the clinical evaluation for conformity assessment purposes, for one or more of the following purposes:

a to establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes listed in point (1) of Article 2, and achieves the performance intended as specified by its manufacturer;

b to establish and verify the clinical benefits of a device as specified by its manufacturer;

c to establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.

2 Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor.

Member States may choose not to apply the first subparagraph to clinical investigations to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical investigation who shall be the addressee for all communications with the sponsor provided for in this Regulation.

3 Clinical investigations shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests and the clinical data generated are scientifically valid, reliable and robust.

Clinical investigations shall be subject to scientific and ethical review. The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a clinical investigation. At least one lay person shall participate in the ethical review.

4 A clinical investigation as referred to in paragraph 1 may be conducted only where all of the following conditions are met:

a the clinical investigation is the subject of an authorisation by the Member State(s) in which the clinical investigation is to be conducted, in accordance with this Regulation, unless otherwise stated;

b an ethics committee, set up in accordance with national law, has not issued a negative opinion in relation to the clinical investigation, which is valid for that entire Member State under its national law;

c the sponsor, or its legal representative or a contact person pursuant to paragraph 2, is established in the Union;

d vulnerable populations and subjects are appropriately protected in accordance with Articles 64 to 68;

e the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;

f 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 Article 63;

g 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;

h 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 Directive 95/46/EC are safeguarded;

i the clinical investigation 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 clinical investigation plan and constantly monitored;

j the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner or any other person entitled by national law to provide the relevant patient care under clinical investigation conditions;

k 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;

l the investigational device(s) in question conform(s) to the applicable general safety and performance requirements set out in Annex I 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 subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art;

m the requirements of Annex XV are fulfilled.

5 Any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the clinical investigation at any time by revoking his or her informed consent. Without prejudice to Directive 95/46/EC, the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

6 The investigator shall be a person exercising a profession which is recognised in the Member State concerned as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.

7 The facilities where the clinical investigation is to be conducted shall be suitable for the clinical investigation and shall be similar to the facilities where the device is intended to be used.

Article 63

Informed consent

1 Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document or the record, as appropriate, by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical investigation.

2 Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

a enable the subject or his or her legally designated representative to understand:

(i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical investigations;

(ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate in and the right to withdraw from the clinical investigation at any time without any resulting detriment and without having to provide any justification;

(iii) the conditions under which the clinical investigations is to be conducted, including the expected duration of the subject's participation in the clinical investigation; and

(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical investigation is discontinued;

b be kept comprehensive, concise, clear, relevant, and understandable to the subject or his or her legally designated representative;

c be provided in a prior interview with a member of the investigating team who is appropriately qualified under national law;

d include information about the applicable damage compensation system referred to in Article 69; and

e include the Union-wide unique single identification number of the clinical investigation referred to in Article 70(1) and information about the availability of the clinical investigation results in accordance with paragraph 6 of this Article.

3 The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

4 In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

5 In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

6 The subject shall be informed that a clinical investigation report and a summary presented in terms understandable to the intended user will be made available pursuant to Article 77(5) in the electronic system on clinical investigations referred to in Article 73 irrespective of the outcome of the clinical investigation, and shall be informed, to the extent possible, when they have become available.

7 This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical investigation.

Article 64

Clinical investigations on incapacitated subjects

1 In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical investigation may be conducted only where, in addition to the conditions set out in Article 62(4), all of the following conditions are met:

a the informed consent of their legally designated representative has been obtained;

b the incapacitated subjects have received the information referred to in Article 63(2) in a way that is adequate in view of their capacity to understand it;

c the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 63(2) to refuse participation in, or to withdraw from, the clinical investigation at any time, is respected by the investigator;

d no incentives or financial inducements are given to subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation;

e the clinical investigation is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical investigations on persons able to give informed consent, or by other research methods;

f the clinical investigation relates directly to a medical condition from which the subject suffers;

g there are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the incapacitated subject outweighing the risks and burdens involved.

2 The subject shall as far as possible take part in the informed consent procedure.

Article 65

Clinical investigations on minors

A clinical investigation on minors may be conducted only where, in addition to the conditions set out in Article 62(4), all of the following conditions are met:

(a) the informed consent of their legally designated representative has been obtained;

(b) the minors have received the information referred to in Article 63(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 63(2) to refuse participation in, or to withdraw from, the clinical investigation at any time, is respected by the investigator;

(d) no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation;

(e) the clinical investigation is intended to investigate treatments for a medical condition that only occurs in minors or the clinical investigation is essential with respect to

minors to validate data obtained in clinical investigations on persons able to give informed consent or by other research methods;

(f) the clinical investigation 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;

(g) there are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the minor subject outweighing the risks and burdens involved;

(h) the minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity;

(i) if during a clinical investigation the minor reaches the age of legal competence to give informed consent as defined in national law, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical investigation.

Article 66

Clinical investigations on pregnant or breastfeeding women

A clinical investigation on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 62(4), all of the following conditions are met:

(a) the clinical investigation 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 research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child;

(c) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation.

Article 67

Additional national measures

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical investigations, or persons in residential care institutions.

Article 68

Clinical investigations in emergency situations

1 By way of derogation from point (f) of Article 62(4), from points (a) and (b) of Article 64(1) and from points (a) and (b) of Article 65, informed consent to participate in a clinical investigation may be obtained, and information on the clinical investigation may be given, after the decision to include the subject in the clinical investigation, provided that that decision is taken at the time of the first intervention on the subject, in accordance with the

clinical investigation plan for that clinical investigation and that all of the following conditions are fulfilled:

a due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical investigation;

b there are scientific grounds to expect that participation of the subject in the clinical investigation will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;

c it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;

d the investigator certifies that he or she is not aware of any objections to participate in the clinical investigation previously expressed by the subject;

e the clinical investigation relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical investigation is of such a nature that it may be conducted exclusively in emergency situations;

f the clinical investigation poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

2 Following an intervention pursuant to paragraph 1 of this Article, informed consent in accordance with Article 63 shall be sought to continue the participation of the subject in the clinical investigation, and information on the clinical investigation shall be given, in accordance with the following requirements:

a regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 63(2) shall be given as soon as possible to the subject and to his or her legally designated representative;

b regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever can be done sooner, and the information referred to in Article 63(2) shall be given as soon as possible to the subject or his or her legally designated representative, as applicable.

For the purposes of point (b) where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical investigation shall be obtained from the subject as soon as he or she is capable of giving informed consent.

3 If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical investigation.

Article 69

Damage compensation

1 Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical investigation conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.

2 The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State in which the clinical investigation is conducted.

Article 70

Application for clinical investigations

1 The sponsor of a clinical investigation shall submit an application to the Member State(s) in which the clinical investigation is to be conducted (referred to for the purposes of this Article as 'Member State concerned') accompanied by the documentation referred to in Chapter II of Annex XV.

The application shall be submitted by means of the electronic system referred to in Article 73, which shall generate a Union-wide unique single identification number for the clinical investigation, which shall be used for all relevant communication in relation to that clinical investigation. Within 10 days of it receiving the application, the Member State concerned shall notify the sponsor as to whether the clinical investigation falls within the scope of this Regulation and as to whether the application dossier is complete in accordance with Chapter II of Annex XV.

2 Within one week of any change occurring in relation to the documentation referred to in Chapter II of Annex XV, the sponsor shall update the relevant data in the electronic system referred to in Article 73 and make that change to the documentation clearly identifiable. The Member State concerned shall be notified of the update by means of that electronic system.

3 Where the Member State concerned finds that the clinical investigation applied for does not fall within the scope of this Regulation or that the application dossier is not complete, it shall inform the sponsor thereof and shall set a time limit of maximum 10 days for the sponsor to comment or to complete the application by means of the electronic system referred to in Article 73. The Member State concerned may extend this period by a maximum of 20 days where appropriate.

Where the sponsor has not provided comments nor completed the application within the time limit referred to in the first subparagraph, the application shall be deemed to have lapsed. Where the sponsor considers the application does fall under the scope of this Regulation and/or is complete but the Member State concerned does not, the application shall be considered to have been rejected. The Member State concerned shall provide for an appeal procedure in respect of such refusal.

The Member State concerned shall notify the sponsor within five days of receipt of the comments or of the requested additional information, whether the clinical investigation is considered as falling within the scope of this Regulation and the application is complete.

4 The Member State concerned may also extend the period referred to in paragraph 1 and 3 each by a further five days.

5 For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 1 or 3 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the periods referred to in paragraphs 1, 3 and 4 respectively.

6 During the period when the application is being assessed, the Member State may request additional information from the sponsor. The expiry of the period laid down in point (b)

of paragraph 7 shall be suspended from the date of the first request until such time as the additional information has been received.

7 The sponsor may start the clinical investigation in the following circumstances:

a in the case of investigational class I devices or in the case of non-invasive class IIa and class IIb devices, unless otherwise stated by national law, immediately after the validation date of the application pursuant to paragraph 5, and provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the clinical investigation;

b in the case of investigational devices, other than those referred to in point (a), as soon as the Member State concerned has notified the sponsor of its authorisation, and provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the clinical investigation. The Member State shall notify the sponsor of the authorisation within 45 days of the validation date referred to in paragraph 5. The Member State may extend this period by a further 20 days for the purpose of consulting with experts.

8 The Commission is empowered to adopt delegated acts in accordance with Article 115 amending, in the light of technical progress and global regulatory developments, the requirements laid down in Chapter II of Annex XV.

9 In order to ensure the uniform application of the requirements laid down in Chapter II of Annex XV, the Commission may adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and of practical application. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 114(3).

Article 71

Assessment by Member States

1 Member States shall ensure that the persons validating and assessing the application, or deciding on it, do not have conflicts of interest, are independent of the sponsor, the investigators involved and of natural or legal persons financing the clinical investigation, as well as free of any other undue influence.

2 Member States shall ensure that the assessment is done jointly by an appropriate number of persons who collectively have the necessary qualifications and experience.

3 Member States shall assess whether the clinical investigation is designed in such a way that potential remaining risks to subjects or third persons, after risk minimization, are justified, when weighed against the clinical benefits to be expected. They shall, while taking into account applicable CS or harmonised standards, examine in particular:

a the demonstration of compliance of the investigational device(s) with the applicable general safety and performance requirements, apart from the aspects covered by the clinical investigation, and whether, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, assurance of technical and biological safety testing and pre-clinical evaluation;

b whether the risk-minimisation solutions employed by the sponsor are described in harmonised standards and, in those cases where the sponsor does not use harmonised standards, whether the risk-minimisation solutions provide a level of protection that is equivalent to that provided by harmonised standards;

c whether the measures planned for the safe installation, putting into service and maintenance of the investigational device are adequate;

d the reliability and robustness of the data generated in the clinical investigation, taking account of statistical approaches, design of the investigation and methodological aspects, including sample size, comparator and endpoints;

e whether the requirements of Annex XV are met;

f in the case of devices for sterile use, evidence of the validation of the manufacturer's sterilisation procedures or information on the reconditioning and sterilisation procedures which have to be conducted by the investigation site;

g the demonstration of the safety, quality and usefulness of any components of animal or human origin or of substances, which may be considered medicinal products in accordance with Directive 2001/83/EC.

4 Member States shall refuse the authorisation of the clinical investigation if:

a the application dossier submitted pursuant to Article 70(1) remains incomplete;

b the device or the submitted documents, especially the investigation plan and the investigator's brochure, do not correspond to the state of scientific knowledge, and the clinical investigation, in particular, is not suitable for providing evidence for the safety, performance characteristics or benefit of the device on subjects or patients,

c the requirements of Article 62 are not met, or

d any assessment under paragraph 3 is negative.

Member States shall provide for an appeal procedure in respect of a refusal pursuant to the first subparagraph.

Article 72

Conduct of a clinical investigation

1 The sponsor and the investigator shall ensure that the clinical investigation is conducted in accordance with the approved clinical investigation plan.

2 In order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical investigation is in compliance with the requirements of this Regulation, the sponsor shall ensure adequate monitoring of the conduct of a clinical investigation. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical investigation including the following:

a the objective and methodology of the clinical investigation; and

b the degree of deviation of the intervention from normal clinical practice.

3 All clinical investigation information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.

4 Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

5 Member States shall inspect, at an appropriate level, investigation site(s) to check that clinical investigations are conducted in accordance with the requirements of this Regulation and with the approved investigation plan.

6 The sponsor shall establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation.

Article 73

Electronic system on clinical investigations

1 The Commission shall, in collaboration with the Member States, set up, manage and maintain an electronic system:

a to create the single identification numbers for clinical investigations referred to in Article 70(1);

b to be used as an entry point for the submission of all applications or notifications for clinical investigations referred to in Articles 70, 74, 75 and 78 and for all other submission of data, or processing of data in this context;

c for the exchange of information relating to clinical investigations in accordance with this Regulation between the Member States and between them and the Commission including the exchange of information referred to in Articles 70 and 76;

d for information to be provided by the sponsor in accordance with Article 77, including the clinical investigation report and its summary as required in paragraph 5 of that Article;

e for reporting on serious adverse events and device deficiencies and related updates referred to in Article 80.

2 When setting up the electronic system referred in paragraph 1 of this Article, the Commission shall ensure that it is interoperable with the EU database for clinical trials on medicinal products for human use set up in accordance with Article 81 of Regulation (EU) No 536/2014 of the European Parliament and of the Council[(1)] as concerns combined clinical investigations of devices with a clinical trial under that Regulation.

3 The information referred to in point (c) of paragraph 1 shall only be accessible to the Member States and the Commission. The information referred to in the other points of that paragraph shall be accessible to the public, unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:

a protection of personal data in accordance with Regulation (EC) No 45/2001;

b protection of commercially confidential information, especially in the investigators brochure, in particular through taking into account the status of the conformity assessment for the device, unless there is an overriding public interest in disclosure;

c effective supervision of the conduct of the clinical investigation by the Member State(s) concerned.

4 No personal data of subjects shall be publicly available.

5 The user interface of the electronic system referred to in paragraph 1 shall be available in all official languages of the Union.

Article 74

Clinical investigations regarding devices bearing the CE marking

1 Where a clinical investigation is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 20(1), ('PMCF investigation'), and where the investigation 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 Member States concerned at least 30 days prior to its commencement by means of the electronic system referred to in Article 73. The sponsor shall include the documentation referred to in Chapter II of Annex XV as part of the notification. Points (b) to (k) and (m) **[**X1of Article 62(4), Articles 75, 76 and 77, and Article 80(5) and (6), and the relevant provisions**]** of Annex XV shall apply to PMCF investigations.

2 Where a clinical investigation is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 20(1), Articles 62 to 81 shall apply.

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).

Article 75

Substantial modifications to clinical investigations

1 If a sponsor intends to introduce modifications to a clinical investigation that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation, it shall notify, within one week, by means of the electronic system referred to in Article 73 the Member State(s) in which the clinical investigation is being or is to be conducted of the reasons for and the nature of those modifications. The sponsor shall include an updated version of the relevant documentation referred to in Chapter II of Annex XV as part of the notification. Changes to the relevant documentation shall be clearly identifiable.

2 The Member State shall assess any substantial modification to the clinical investigation in accordance with the procedure laid down in Article 71.

3 The sponsor may implement the modifications referred to in paragraph 1 at the earliest 38 days after the notification referred to in that paragraph, unless:

a the Member State in which the clinical investigation is being or is to be conducted has notified the sponsor of its refusal based on the grounds referred to in Article 71(4) or on considerations of public health, subject and user safety or health, of public policy, or

b an ethics committee in that Member State has issued a negative opinion in relation to the substantial modification to the clinical investigation, which, in accordance with national law, is valid for that entire Member State.

4 The Member State(s) concerned may extend the period referred to in paragraph 3 by a further seven days, for the purpose of consulting with experts.

Article 76

Corrective measures to be taken by Member States and information exchange between Member States

1 Where a Member State in which a clinical investigation is being or is to be conducted has grounds for considering that the requirements set out in this Regulation are not met, it may take at least any of the following measures on its territory:

a revoke the authorisation for the clinical investigation;

b suspend or terminate the clinical investigation;

c require the sponsor to modify any aspect of the clinical investigation.

2 Before the Member State concerned takes any of the measures referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor or the investigator or both for their opinion. That opinion shall be delivered within seven days.

3 Where a Member State has taken a measure referred to in paragraph 1 of this Article or has refused a clinical investigation, or has been notified by the sponsor of the early termination of a clinical investigation on safety grounds, that Member State shall communicate the corresponding decision and the grounds therefor to all Member States and the Commission by means of the electronic system referred to in Article 73.

4 Where an application is withdrawn by the sponsor prior to a decision by a Member State, that information shall be made available through the electronic system referred to in Article 73 to all Member States and the Commission.

Article 77

Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination

1 If the sponsor has temporarily halted a clinical investigation or has terminated a clinical investigation early, it shall inform within 15 days the Member State in which that clinical investigation has been temporarily halted or terminated early, through the electronic system referred to in Article 73, of the temporary halt or early termination, providing a justification. In the event that the sponsor has temporarily halted or terminated early the clinical investigation on safety grounds, it shall inform all Member States in which that clinical investigation is being conducted thereof within 24 hours.

2 The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end is set out in the clinical investigation plan.

3 The sponsor shall notify each Member State in which a clinical investigation was being conducted of the end of that clinical investigation in that Member State. That notification shall be made within 15 days of the end of the clinical investigation in relation to that Member State.

4 If an investigation is conducted in more than one Member State, the sponsor shall notify all Member States in which that clinical investigation was conducted of the end of the clinical investigation in all Member States. That notification shall be made within 15 days of that end of the clinical investigation.

5 Irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, the sponsor shall submit to the Member States in which a clinical investigation was conducted a clinical investigation report as referred to in Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV.

The clinical investigation report shall be accompanied by a summary presented in terms that are easily understandable to the intended user. Both the report and summary shall be submitted by the sponsor by means of the electronic system referred to in Article 73.

Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation, it shall be submitted as soon as it is available. In such case, the clinical investigation plan referred to in Section 3 of Chapter II of Annex XV shall specify when the results of the clinical investigation are going to be available, together with a justification.

6 The Commission shall issue guidelines regarding the content and structure of the summary of the clinical investigation report.

In addition, the Commission may issue guidelines for the formatting and sharing of raw data, for cases where the sponsor decides to share raw data on a voluntary basis. Those guidelines may take as a basis and adapt, where possible, existing guidelines for sharing of raw data in the field of clinical investigations.

7 The summary and the clinical investigation report referred to in paragraph 5 of this Article shall become publicly accessible through the electronic system referred to in Article 73, at the latest when the device is registered in accordance with Article 29 and before it is placed on the market. In cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission.

If the device is not registered in accordance with Article 29 within one year of the summary and the report having been entered into the electronic system pursuant to paragraph 5 of this Article, they shall become publicly accessible at that point in time.

Article 78

Coordinated assessment procedure for clinical investigations

1 By means of the electronic system referred to in Article 73, the sponsor of a clinical investigation to be conducted in more than one Member State may submit, for the purpose of Article 70, a single application that, upon receipt, is transmitted electronically to all Member States in which the clinical investigation is to be conducted.

2 The sponsor shall propose in the single application referred to in paragraph 1 that one of the Member States in which the clinical investigation is to be conducted acts as coordinating Member State. The Member States in which the clinical investigation is to be conducted shall, within six days of submission of the application, agree on one of them taking the role of the coordinating Member State. If they do not agree on a coordinating Member State, the coordinating Member State proposed by the sponsor shall assume that role.

3 Under the direction of the coordinating Member State referred to in paragraph 2, the Member States concerned shall coordinate their assessment of the application, in particular of the documentation referred to in Chapter II of Annex XV.

However, the completeness of the documentation referred to in Sections 1.13, 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XV shall be assessed separately by each Member State concerned in accordance with Article 70(1) to (5).

4 With regard to documentation other than that referred to in the second subparagraph of paragraph 3, the coordinating Member State shall:

a within six days of receipt of the single application, notify the sponsor that it is the coordinating Member State (‘notification date’);

b for the purpose of the validation of the application, take into account any considerations submitted within seven days of the notification date by any Member State concerned;

c within 10 days of the notification date, assess whether the clinical investigation falls within the scope of this Regulation and whether the application is complete, and shall notify the sponsor accordingly. Article 70(1) and (3) to (5) shall apply to the coordinating Member State in relation to that assessment;

d establish the results of its assessment in a draft assessment report to be transmitted within 26 days of the validation date to the Member States concerned. By day 38 after the validation date, the other Member States concerned shall transmit their comments and proposals on the draft assessment report and the underlying application to the coordinating Member State which shall take due account of those comments and proposals in its finalisation of the final assessment report, to be transmitted within 45 days of the validation date to the sponsor and the other Member States concerned.

The final assessment report shall be taken into account by all Member States concerned when deciding on the sponsor's application in accordance with Article 70(7).

5 As regards the assessment of the documentation referred to in the second subparagraph of paragraph 3, each Member State concerned may request, on a single occasion, additional information from the sponsor. The sponsor shall submit the requested additional information within the period set by the Member State concerned, which shall not exceed 12 days from the receipt of the request. The expiry of the last deadline pursuant to point (d) of paragraph 4 shall be suspended from the date of the request until such time as the additional information has been received.

6 For class IIb and class III devices, the coordinating Member State may also extend the periods referred to in paragraph 4 by a further 50 days, for the purpose of consulting with experts.

7 The Commission may, by means of implementing acts, further specify the procedures and timescales for coordinated assessments to be taken into account by Member States concerned when deciding on the sponsor's application. Such implementing acts may also set out the procedures and timescales for coordinated assessment in the case of substantial modifications pursuant to paragraph 12 of this Article, in the case of reporting of adverse events pursuant to Article 80(4) and in the case of clinical investigations of combination products between medical devices and medicinal products, where the latter are under a concurrent coordinated assessment of a clinical trial under Regulation (EU) No 536/2014. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 114(3).

8 Where the conclusion of the coordinating Member State concerning the area of coordinated assessment is that the conduct of the clinical investigation is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of all Member States concerned.

Notwithstanding the first subparagraph, a Member State concerned may only disagree with the conclusion of the coordinating Member State concerning the area of coordinated assessment on the following grounds:

a when it considers that participation in the clinical investigation would lead to a subject receiving treatment inferior to that received in normal clinical practice in that Member State concerned;

b infringement of national law; or

[[X2]c considerations as regards subject safety and data reliability and robustness submitted under point (d) of paragraph 4.**]**

Where one of the Member States concerned disagrees with the conclusion on the basis of the second subparagraph of this paragraph, it shall communicate its disagreement, together with a detailed justification, through the electronic system referred to in Article 73, to the Commission, to all other Member States concerned and to the sponsor.

9 Where the conclusion of the coordinating Member State concerning the area of coordinated assessment is that the clinical investigation is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

10 A Member State concerned shall refuse to authorise a clinical investigation if it disagrees with the conclusion of the coordinating Member State as regards any of the grounds referred to in the second subparagraph of paragraph 8, or if it finds, on duly justified grounds, that the aspects addressed in Sections 1.13, 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XV are not complied with, or where an ethics committee has issued a negative opinion in relation to that clinical investigation, which is valid, in accordance with national law, for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

11 Each Member State concerned shall notify the sponsor through the electronic system referred to in Article 73 as to whether the clinical investigation is authorised, whether it is authorised subject to conditions, or whether authorisation has been refused. Notification shall be done by way of one single decision within five days of the transmission, pursuant to point (d) of paragraph 4, by the coordinating Member State of the final assessment report. Where an authorisation of a clinical investigation is subject to conditions, those conditions may only be such that, by their nature, they cannot be fulfilled at the time of that authorisation.

12 Any substantial modifications as referred to in Article 75 shall be notified to the Member States concerned by means of the electronic system referred to in Article 73. Any assessment as to whether there are grounds for disagreement as referred to in the second subparagraph of paragraph 8 of this Article shall be carried out under the direction of the coordinating Member State, except for substantial modifications concerning Sections 1.13, 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XV, which shall be assessed separately by each Member State concerned.

13 The Commission shall provide administrative support to the coordinating Member State in the accomplishment of its tasks under this Chapter.

[[X1]14 The procedure set out in this Article shall, until 25 May 2027, be applied only by those of the Member States in which the clinical investigation is to be conducted which have agreed to apply it. From 26 May 2027, all Member States shall be required to apply that procedure.**]**

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).

X2 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).

Article 79

Review of coordinated assessment procedure

By 27 May 2026, the Commission shall submit to the European Parliament and to the Council a report on experience gained from the application of Article 78 and, if necessary, propose a review of Article 78(14) and point (h) of Article 123(3).

Article 80

Recording and reporting of adverse events that occur during clinical investigations

1 The sponsor shall fully record all of the following:

a 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;

b any serious adverse event;

c 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 any new findings in relation to any event referred to in points (a) to (c).

2 The sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following by means of the electronic system referred to in Article 73:

a any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

b 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;

c any new findings in relation to any event referred to in points (a) and (b).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all information referred to in paragraph 1.

3 The sponsor shall also report to the Member States in which the clinical investigation is being conducted any event referred to in paragraph 2 of this Article that occurred in third countries in which a clinical investigation is performed under the same clinical investigation plan as the one applying to a clinical investigation covered by this Regulation by means of the electronic system referred to in Article 73.

4 In the case of a clinical investigation for which the sponsor has used the single application referred to in Article 78, the sponsor shall report any event as referred to in paragraph 2 of this Article by means of the electronic system referred to in Article 73. Upon receipt, this report shall be transmitted electronically to all Member States in which the clinical investigation is being conducted.

Under the direction of the coordinating Member State referred to in Article 78(2), the Member States shall coordinate their assessment of serious adverse events and device deficiencies to determine whether to modify, suspend or terminate the clinical investigation or whether to revoke the authorisation for that clinical investigation.

This paragraph shall not affect the rights of the other Member States to perform their own evaluation and to adopt measures in accordance with this Regulation in order to ensure the protection of public health and patient safety. The coordinating Member State and the Commission shall be kept informed of the outcome of any such evaluation and the adoption of any such measures.

5 In the case of PMCF investigations referred to in Article 74(1), the provisions on vigilance laid down in Articles 87 to 90 and in the acts adopted pursuant to Article 91 shall apply instead of this Article.

6 Notwithstanding paragraph 5, this Article shall apply where a causal relationship between the serious adverse event and the preceding investigational procedure has been established.

Article 81

Implementing acts

The Commission may, by means of implementing acts, establish the detailed arrangements and procedural aspects necessary for the implementation of this Chapter as regards the following:

(a) harmonised electronic forms for the application for clinical investigations and their assessment as referred to in Articles 70 and 78, taking into account specific categories or groups of devices;

(b) the functioning of the electronic system referred to in Article 73;

(c) harmonised electronic forms for the notification of PMCF investigations as referred to in Article 74(1), and of substantial modifications as referred to in Article 75;

(d) the exchange of information between Member States as referred to in Article 76;

(e) harmonised electronic forms for the reporting of serious adverse events and device deficiencies as referred to in Article 80;

(f) the timelines for the reporting of serious adverse events and device deficiencies, taking into account the severity of the event to be reported as referred to in Article 80;

(g) uniform application of the requirements regarding the clinical evidence or data needed to demonstrate compliance with the general safety and performance requirements set out in Annex I.

The implementing acts referred to in the first paragraph shall be adopted in accordance with the examination procedure referred to in Article 114(3).

Article 82

Requirements regarding other clinical investigations

1 Clinical investigations, not performed pursuant to any of the purposes listed in Article 62(1), shall comply with the provisions of Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6).

2 In order to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations not performed for any of the purposes listed in Article 62(1), each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned.

(**1**) Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

Status:
Point in time view as at 05/05/2017.

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