



STATUTORY INSTRUMENTS.

S.I. No. 99 of 2022

EUROPEAN UNION (CLINICAL TRIALS ON MEDICINAL PRODUCTS
FOR HUMAN USE) (PRINCIPAL) REGULATIONS 2022

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I, STEPHEN DONNELLY, Minister for Health, in exercise of the powers conferred on me by section 3 of the European Communities Act 1972 (No. 27 of 1972) and for the purpose of giving further effect to Regulation (EC) No. 536/2014 of 16 April 2014¹, hereby make the following regulations:

PART 1
PRELIMINARY

Citation

1. These Regulations may be cited as the European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022.

2. (1) These Regulations apply to all clinical trials conducted in the State.
(2) These Regulations do not apply to non-interventional studies.

Interpretation

3. (1) In these Regulations—
“Advisory Committee for Human Medicines” means the committee established by section 9 of the Irish Medicines Board Act 1995 (No. 29 of 1995), as amended;
“Agency” means the European Medicines Agency, established by Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004²;
“Assessment Report” means the report required to be drawn up by the reporting Member State or the Member State concerned, as appropriate, in the context of an application for a clinical trial under Article 6(2) and Article 7(2) of the Clinical Trials Regulation.
“Authority” means the Health Products Regulatory Authority established by section 3 of the Irish Medicines Board Act 1995 (No. 29 of 1995), as amended;
“Clinical Trials Regulation” means Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014¹ on clinical trials on medicinal products for human use;

¹ O.J. No. L 158, 27.5.2014, p. 1.

² O.J. No. L 136, 30.4.2004, p. 1.

“Commission Delegated Regulation (EU) 2017/1569” means Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017³;

“clinical study” has the same meaning as it has in the Clinical Trials Regulation;
“clinical trial” has the same meaning as it has in the Clinical Trials Regulation;

“Data Protection Acts 1988 to 2018” means the Data Protection Act 1988 (No. 25 of 1988), the Data Protection Act 2003 (No. 6 of 2003) and the Data Protection Act 2018 (No. 7 of 2018);

“Declaration of Helsinki” means the Declaration of Helsinki adopted by the General Assembly of the World Medical Association in June 1964, and as amended by the General Assembly of that Association from time to time;

“Directive” means Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001⁴;

“Directive 2001/83/EC⁶” means Directive 2001/83/EC of the European Parliament and of the Council;

“EU database” means the database established under Article 81 of the Clinical Trials Regulation;

“EU portal” means the electronic portal established under Article 80 of the Clinical Trials Regulation;

“EudraGMDP database” means the EU database, maintained and operated by the European Medicines Agency, on manufacturing, import and wholesale-distribution authorisations, and good manufacturing-practice (GMP) and good-distribution-practice (GDP) certificates;

“General Data Protection Regulation” means Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016⁵;

“incapacitated subject” means a subject who is, for reasons other than the age of legal competence to give informed consent, incapable of giving informed consent to participate in a clinical trial;

“investigator” for the purposes of Article 49 of the Clinical Trials Regulation and these Regulations means -

- (a) a medical practitioner within the meaning of section 2 of the Medical Practitioners Act 2007 (No. 25 of 2007),
- (b) a visiting EEA practitioner within the meaning of section 2 of the Medical Practitioners Act 2007, or
- (c) a registered dentist within the meaning of section 2 of the Dentists Act 1985 (No. 9 of 1985);

“Joint Controllership Arrangement” means the arrangement agreed by the European Commission, European Medicines Agency, Member States, sponsors

³ O.J. No. L 238, 16.9.2017, p. 12.

⁴ O.J. No. L 121, 1.5.2001, p. 34.

⁵ O.J. No. L 119, 4.5.2016, p. 1.

⁶ O.J. No. L 311, 28.11.2001, p. 67

and marketing authorisation applicants or holders for the purpose of processing personal data captured in the EU portal;

“legally designated representative”, for the purposes of these Regulations and the Clinical Trials Regulation only, means—

- (a) in relation to an incapacitated subject who is, or is being considered as, a subject for a clinical trial—
 - (i) a person, other than a person connected with the conduct of the trial, who by virtue of his or her family or other personal relationship with the individual—
 - (aa) can provide the best interpretation of the will and preferences of the individual based on their knowledge of the individual,
 - (bb) is available and willing to act for that purpose, or
 - (ii) if there is no such person, the medical practitioner primarily responsible for the medical treatment provided to the individual where he or she—
 - (aa) can provide the best interpretation of the will and preferences of the individual based on their knowledge of the individual,
 - (bb) is not involved in the conduct of the trial,
 - (cc) is of the view that participation in the trial will not prejudice the health and wellbeing of the individual, and
 - (dd) is available and willing to act for that purpose, and
- (b) in relation to a minor who is, or is being considered as, a subject for a clinical trial, a guardian within the meaning of the Guardianship of Infants Act 1964 (No. 7 of 1964);

“legal representative” means the natural or legal person established in the European Union as the legal representative of a clinical trial sponsor who is not established in the Union;

“manufacturer’s authorisation” means an authorisation for the manufacture or import of investigational medicinal products referred to in Article 61(1) of the Clinical Trials Regulation which is for the time being in force and which has been granted by the Authority pursuant to Regulation 38;

“marketing authorisation” means an authorisation which is for the time being in force and which has been granted by the Authority under the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007), or by the Commission under Regulation (EC) No. 726/2004² and includes a marketing authorisation issued by the competent authority of an EEA State, other than the State, in accordance with Directive 2001/83/EC⁶;

“medical doctor” for the purpose of Article 49 of the Clinical Trials Regulation means a registered medical practitioner;

“Minister” means the Minister for Health;

“minor” means a person under the age of 16 years;

“National Office” has the meaning assigned to it by Regulation 5 of the European Union Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022 (S.I. No. 41 of 2022);

“National Research Ethics Committee” has the meaning assigned to it by Regulation 13 of the European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022 (S.I. No. 41 of 2022);

“nominated ethics committee” means the National Research Ethics Committee nominated by the National Office to assess and provide an opinion on a specific clinical trial application, or substantial modification to a clinical trial granted authorisation, pursuant to the Clinical Trials Regulation;

“non-commercial sponsor” means a sponsor who has no commercial or financial interest in the outcome of the clinical trial;

“non-commercial clinical trial” means a clinical trial conducted by a non-commercial sponsor which fulfils the following characteristics—

- (a) the ownership of the investigation data belongs to the non-commercial sponsor from the inception of the clinical trial, and
- (b) the design, conduct, recruitment, recording of data and reporting of the results of the investigation remain under the control of the non-commercial sponsor;

“Part I” refers to Part I of the Assessment Report;

“Part II” refers to Part II of the Assessment Report;

“premises” means any place (physical or virtual), ship or other vessel, aircraft, railway wagon or other vehicle or other mobile facility, other than a dwelling, and includes a container used to transport an investigational medicinal product and/or an auxiliary medicinal product or other relevant thing;

“qualified person” means a person with the qualifications and experience specified in Article 49(2) and (3) of Directive 2001/83/EC⁶ and named in the manufacturer’s authorisation as being responsible for the functions set out in Article 62 of the Clinical Trials Regulation;

“relevant health care provider” means –

- (a) in relation to a person receiving services in pursuance of the Health Acts 1947 to 2007—
 - (i) in a case where a health service body is providing the health care, that body, or
 - (ii) in any other case, the health service body which entered the arrangements under which the health care is provided, or
- (b) in relation to any other person receiving health care, the person primarily responsible for providing that health care;

“registered nurse” means a person registered in the Register of Nurses and Midwives established under section 46(1)(a) of the Nurses and Midwives Act 2011 (No. 41 of 2011);

“registered pharmacist” means a person registered in the Register of Pharmacists established under section 13(1) of the Pharmacy Act 2007 (No. 20 of 2007);

“Register of Exemptions” means the register of processes specified in Article 61(6) of the Clinical Trials Regulation which are exempt from the requirements of Article 61(1) and which is established under Regulation 30 herein;

“Regulation (EC) No 726/2004²” means regulations of the European Parliament and of the Council of 31 March 2004;

“Regulation (EU) 2017/556⁷” means Commission Implementing Regulation (EU) 2017/556 of 24 March 2017;

“reporting Member State” means the Member State concerned appointed as reporting Member State under Article 5 of the Clinical Trials Regulation;

“subject” means an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control;

“S.I. No. 40 of 2022” means the European Union (Clinical Trials on Medicinal Products for Human Use) Regulations 2022;

“S.I. No. 41 of 2022” means the European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022;

(2) A word or expression which is used in these Regulations and which is also used in the Clinical Trials Regulation has, unless the context otherwise requires, the same meaning in these Regulations as it has in the Clinical Trials Regulation.

Roles of Authority, National Office and Nominated Ethics Committee

4. (1) Save as may be otherwise expressly provided for in these Regulations and subject to paragraph (2)—

(a) the role of Member State, pursuant to the Clinical Trials Regulation, shall be carried out by the Authority and the National Office in conjunction with the nominated ethics committee, each of which—

(i) may communicate information when carrying out their respective functions under the Clinical Trials Regulation, and

(ii) shall keep such communications confidential,

(b) where the State is the reporting Member State under the Clinical Trials Regulation, the Authority and the National Office in conjunction with the nominated ethics committee shall co-ordinate in the review of applications for the conduct of clinical

⁷ O.J. No. L 80, 25.3.2017, p. 7.

- trials and applications for substantial modifications to clinical trials granted authorisation, and perform the functions ascribed to the reporting Member State under the Clinical Trials Regulation within the timelines set out therein,
- (c) where the State is a Member State concerned under the Clinical Trials Regulation, the Authority and the National Office in conjunction with the nominated ethics committee shall perform the functions ascribed to the Member State concerned under the Clinical Trials Regulation within the timelines set out therein,
 - (d) where the State is an additional Member State concerned pursuant to Article 14 of the Clinical Trials Regulation, the Authority and the National Office in conjunction with the nominated ethics committee shall perform the functions ascribed to additional Member States concerned under the Clinical Trials Regulation within the timelines set out therein, and
 - (e) notifications to the EU portal envisaged at Article 80 of the Clinical Trials Regulation and submissions to the EU database envisaged at Article 81 thereof shall be made by either the Authority or the National Office, as appropriate.
 - (f) the Authority shall—
 - (i) perform the scientific review referred to in Article 4 of the Clinical Trials Regulation,
 - (ii) validate the aspects covered by the Part I assessment, pursuant to Chapters II and III of the Clinical Trials Regulation,
 - (iii) be the national contact point for the purposes of Article 83 of the Clinical Trials Regulation,
 - (iv) perform the inspections envisaged by Articles 63 and 78 of the Clinical Trials Regulation,
 - (v) collect the fees envisaged by Chapter XVI of the Clinical Trials Regulation,
 - (vi) be responsible for the enforcement of these Regulations and the prosecution of any offences thereunder.
 - (g) the National Office, in conjunction with the nominated ethics committee, shall—
 - (i) perform the ethical review referred to in Article 4 of the Clinical Trials Regulation,
 - (ii) validate the aspects covered by the Part II assessment, pursuant to Chapters II and III of the Clinical Trials Regulation.
 - (h) the National Office shall have the additional functions described in S.I. No. 41 of 2022.
 - (i) a National Research Ethics Committee shall have the additional functions described in S.I. No. 41 of 2022.

(2) The Minister may publish guidelines as to the appropriate division of tasks prescribed by the Clinical Trials Regulation, between the Authority, the National Office and the nominated ethics committee, as appropriate.

PART 2

AUTHORISATION TO CONDUCT CLINICAL TRIALS AND AUTHORISATION OF SUBSTANTIAL MODIFICATIONS TO CLINICAL TRIALS GRANTED AUTHORISATION

Determination on role as a reporting Member State

5. (1) Subject to paragraph (2), the Authority shall determine whether the State is willing to be the reporting Member State pursuant to Article 5(1) of the Clinical Trials Regulation, or not, and shall notify any decision to all Member States concerned through the EU Portal.

(2) Before making its determination under paragraph (1), the Authority shall consult with the National Office.

Determination on scope of application

6. The Authority shall assess whether the application for authorisation is within the scope of the Clinical Trials Regulation as envisaged by Article 5(3)(a) thereof.

Drafting of Reports

7. Subject to the requirements of Regulations 8, 9, and 12, the Authority shall draft Part I of the Assessment Report, and the National Office in conjunction with the nominated ethics committee shall draft Part II of the Assessment Report, and they shall coordinate with each other, as appropriate, to ensure the production of the final Report.

Assessment of application – Part I of Assessment Report

8. (1) Subject to paragraph (2), the Authority shall—

- (a) review the application in terms of the scientific aspects covered by Part I of the Assessment Report,
- (b) draw up Part I of the Assessment Report under Article 6(2) of the Clinical Trials Regulation, and
- (c) conclude on the application insofar as Part I of the Assessment Report is concerned, under Article 6(4) of the Clinical Trials Regulation.

(2) In order to assist the Authority in the performance of its functions under paragraph (1)(b) and (1)(c), the nominated ethics committee shall—

- (a) review the application in terms of the ethical aspects of the matters covered by Part I of the Assessment Report, and
- (b) provide input to the Authority on those ethical aspects, in accordance with Regulation 19 of S.I. No. 41 of 2022.

Assessment of application – Part II of Assessment Report

9. The National Office and the nominated ethics committee shall—
 - (1) review the application in terms of the matters covered by Part II of the Assessment Report,
 - (2) draw up part II of the Assessment Report under Article 7(1) of the Clinical Trials Regulation in accordance with Regulation 7, and
 - (3) conclude on Part II of the Assessment Report under Article 7(2) of the Clinical Trials Regulation.

Grant or refusal of application

10. (1) In accordance with Article 8(1) or Article 14(3) of the Clinical Trials Regulation, as appropriate, the Authority shall issue an administrative single decision, through the EU portal, as to whether—
 - (a) a clinical trial is authorised,
 - (b) a clinical trial is authorised subject to certain conditions, or
 - (c) authorisation of a clinical trial is refused.
- (2) Authorisation of a clinical trial shall be refused pursuant to Article 8(4) or Article 14(10) of the Clinical Trials Regulation, as appropriate, where—
 - (a) the Authority or the nominated ethics committee disagrees with the reporting Member State's conclusion as regards Part I of the Assessment Report on any of the grounds stated in the second subparagraph of Article 8(2) or Article 14(4) of the Clinical Trials Regulation, as appropriate,
 - (b) the nominated ethics committee finds on duly justified grounds, that the aspects addressed in Part II of the Assessment Report are not complied with, or
 - (c) the nominated ethics committee has issued a negative opinion in relation to the application.

Validation of application for authorisation of a substantial modification

11. (1) The Authority shall validate the application for a substantial modification and notify the sponsor of the matters at Article 17(2)(a) and (b) of the Clinical Trials Regulation, where the substantial modification concerns—
 - (a) an aspect covered by Part I of the Assessment Report as envisaged by Article 17 of the Clinical Trials Regulation, or

- (b) aspects covered by Parts I and II of the Assessment Report, as envisaged by Article 21 of the Clinical Trials Regulation.
- (2) The National Office in conjunction with the nominated ethics committee shall validate the application and notify the sponsor of the matters at Article 20(1)(a) and (b) of the Clinical Trials Regulation, where the substantial modification concerns an aspect covered by Part II of the Assessment Report.

Assessment of application for authorisation of a substantial modification

12. The following procedure shall apply in relation to the assessment of an application for authorisation of a substantial modification—

(1) the Authority shall perform the scientific review of the Part I assessment in accordance with Articles 18 and 21, as appropriate, of the Clinical Trials Regulation,

(2) in order for the Authority to conclude on the Part I assessment, the National Office, in conjunction with the nominated ethics committee, shall provide an opinion following ethical review of Part I, pursuant to Article 18 or 21 of the Clinical Trials Regulation and Regulation 19 of S.I. No. 41 of 2022;

(3) the Authority shall conclude on the Part I assessment in accordance with Article 19 or 23 of the Clinical Trials Regulation, as appropriate,

(4) the nominated ethics committee shall review and conclude on the Part II assessment in accordance with Article 20 or Article 23 of the Clinical Trials Regulation, as appropriate,

(5) the Authority shall submit an administrative single decision on a substantial modification application for authorisation, in accordance with Articles 19 or 23 of the Clinical Trials Regulation,

(6) the National Office shall submit an administrative single decision on a substantial modification application for authorisation in accordance with Article 20 of the Clinical Trials Regulation.

Grant or refusal of application for authorisation of a substantial modification

13. (1) In accordance with Article 19(1) of the Clinical Trials Regulation and where the substantial modification concerns an aspect covered by Part I of the Assessment Report, the Authority shall notify the sponsor through the EU portal as to whether—

- (a) the substantial modification is authorised,
- (b) the substantial modification is authorised subject to certain conditions,
- (c) authorisation of the substantial modification is refused.

(2) In accordance with Article 20(5) of the Clinical Trials Regulation and where the substantial modification concerns an aspect covered by Part II of the Assessment Report, the National Office (through the Authority if required by the operation of the EU portal) shall notify the sponsor through the EU portal as to whether—

- (a) the substantial modification is authorised,
 - (b) the substantial modification is authorised subject to conditions allowable under Article 20(5) of the Clinical Trials Regulation,
 - (c) authorisation of the substantial modification is refused.
- (3) In accordance with Article 23(1) of the Clinical Trials Regulation and where the modification concerns an aspect covered by Parts I and II of the Assessment Report, the National Office will co-ordinate with the Authority to ensure that the sponsor is notified of the nominated ethics committee's decision under Article 22 of the Clinical Trials Regulation, to facilitate notification in accordance with a method prescribed under Article 20(5) of the Clinical Trials Regulation
- (4) Authorisation of a substantial modification of an aspect covered by Part I of the Assessment Report shall be refused pursuant to Article 19(2), where—
- (a) the Authority or the nominated ethics committee disagrees with the reporting Member State's conclusions as regards Part I of the Assessment Report, on any of the grounds stated in the second subparagraph of Article 19(2) of the Clinical Trials Regulation, or,
 - (b) the nominated ethics committee has issued a negative opinion in relation to the substantial modification,
- (5) Authorisation of a substantial modification of an aspect covered by Part II of the Assessment Report shall be refused pursuant to Article 20(7) of the Clinical Trials Regulation, where—
- (a) the nominated ethics committee finds that aspects covered by Part II of the Assessment Report are not complied with, or
 - (b) the nominated ethics committee has issued a negative opinion in accordance with Article 20(7) of the Clinical Trials Regulation.
- (6) Authorisation of a substantial modification of an aspect covered by Part I and Part II of the Assessment Report shall be refused where—
- (a) the Authority or nominated ethics committee disagrees with the reporting Member State's conclusions as regards Part I of the Assessment Report, on any of the grounds stated in the second subparagraph of Article 23(2) of the Clinical Trials Regulation,
 - (b) the nominated ethics committee finds, on duly justified grounds, that the aspects covered by Part II of the Assessment Report are not complied with, or
 - (c) the nominated ethics committee has issued a negative opinion in relation to the substantial modification.

PART 3
CONDUCT OF CLINICAL TRIALS

Conduct of clinical trials within the State

14. (1) Without prejudice to the Clinical Trials Regulation, a person shall not—

- (a) conduct a clinical trial,
- (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), or
- (c) perform the functions of the investigator of a clinical trial,

in the State, otherwise than in accordance with paragraph (2).

(2) The activities at paragraph 1(a) to (c) shall be conducted in accordance with—

- (a) the Clinical Trials Regulation,
- (b) these Regulations,
- (c) the Declaration of Helsinki,
- (d) the authorisation to conduct that clinical trial as notified to the sponsor under Regulation 10 or 13 of these Regulations,
- (e) any clinical trial protocol relating to a particular clinical trial,
- (f) any particulars or documents, other than the clinical trial protocol, accompanying a clinical trial application, as may be modified from time to time in accordance with Articles 17 to 23 of the Clinical Trials Regulation,
- (g) the conditions and principles of good clinical practice, and
- (h) any other relevant guidance, including guidance published by the Agency or the European Commission.

Compliance with obligations where the sponsor is not established in European Union

15. Where a natural or legal person is established in the European Union as the legal representative of a sponsor not established in the Union in accordance with Article 74(1) of the Clinical Trials Regulation, that representative shall be responsible for ensuring compliance with the sponsor's obligations in the State, pursuant to the Clinical Trials Regulation and these Regulations.

Charges to subjects of clinical trials

16. (1) Subject to paragraph (2) and for the purposes of Article 92 of the Clinical Trials Regulation, the sponsor of a clinical trial shall ensure that—

- (a) any investigational medicinal products or auxiliary medicinal products used in the clinical trial, and

(b) any medical devices used for the administration of such products, are made available free of charge to the subject of the clinical trial.

(2) Paragraph (1) shall not apply to a non-commercial clinical trial conducted by a non-commercial sponsor, except in circumstances where the sponsor has obtained the products or devices referred to in paragraph (1) free of charge, in which case clinical trial subjects shall not bear any cost relating to such products or devices.

Damage compensation

17. A clinical trial shall not be authorised under these Regulations, or conducted in the State, unless there is in place a policy of insurance or indemnity scheme to provide compensation for any damage suffered by a subject resulting from participation in the clinical trial, which policy or scheme shall be appropriate to the nature and the extent of the risk.

PART 4

PROTECTION OF CLINICAL TRIAL SUBJECTS AND INFORMED CONSENT

General rules, emergency rules

18. (1) Subject to paragraph (3), a clinical trial shall not be conducted in the State other than in accordance with the general rules laid down in Article 28 of the Clinical Trials Regulation.

(2) For the purposes of Article 28(1)(d), national law in relation to privacy and data rights of individuals shall also apply, in particular the Data Protection Acts 1988 to 2018.

(3) Article 28(1)(b) and (c), Article 31(1)(a) and (b), and Article 32(1)(a) and (b) of the Clinical Trials Regulation may be derogated from in emergency situations in the manner prescribed by Article 35 of the Clinical Trials Regulation.

Informed consent, consent in cluster trials

19. (1) For clinical trials in the State, informed consent shall be given or obtained in accordance with Article 29 of the Clinical Trials Regulation.

(2) For clinical trials in the State, the interview prescribed by Article 29(2)(c) of the Clinical Trials Regulation shall be conducted by the investigator or by—

- (a) a registered medical practitioner,
- (b) a registered dentist, or
- (c) a registered nurse

whose training, experience and qualifications have been assessed by the investigator and determined to be appropriate to qualify him, or her, to conduct the interview.

(3) For the purposes of Article 29(8) of the Clinical Trials Regulation, in addition to the informed consent given by a guardian, 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 trial.

(4) For clinical trials which are to be conducted exclusively in the State, the investigator may obtain informed consent by simplified means, in accordance with Article 30 of the Clinical Trials Regulation, provided all conditions therein are met.

PART 5

CLINICAL TRIAL MASTER FILE AND ARCHIVING

Trial master file

20. Without prejudice to the general obligations on sponsors and investigators under Article 57 of the Clinical Trials Regulation in relation to the keeping of a clinical trial master file, the clinical trial master file shall—

(1) contain information—

- (a) sufficient to demonstrate whether the principles and guidelines of good clinical practice, Annex I and, where applicable, Annex II to the Clinical Trials Regulation, have been complied with, and
- (b) which is specific to each phase of the clinical trial,

(2) be readily available for inspection by the Authority and directly accessible upon request, and

(3) form the basis for the Authority's inspection as envisaged by Article 78 of the Clinical Trials Regulation.

Archiving

21. Without prejudice to the general obligations on sponsors and investigators under Article 58 of the Clinical Trials Regulation in relation to archiving—

(1) the clinical trial master file shall be archived—

- (a) for at least 25 years after the end of a clinical trial, or such longer period as may be agreed between the sponsor and investigator, and
- (b) in a manner which ensures that it can be made available for inspection by the Authority.

(2) the medical files of trial subjects shall be retained for the maximum period of time permitted or required by the hospital, entity, or private practice at which the trial is conducted.

PART 6

SUPERVISION AND CONTROL

Inspections in the State

22. The Authority and the National Office in conjunction with the nominated ethics committee shall supervise clinical trials authorised for conduct in the State, and may communicate with each other in regard to same. All such communications shall be confidential.

23. The Authority is designated as the competent authority for inspections pursuant to Article 78 of the Clinical Trials Regulation and shall carry out the functions of the competent authority in that regard.

Corrective measures

24. (1) Subject to paragraphs (3) and (4), where the State is a Member State concerned and the Authority has justified grounds for considering that the requirements set out in the Clinical Trials Regulation are no longer met, the Authority may take any corrective measure set out under Article 77(1) of the Clinical Trials Regulation, in accordance with the procedure set out therein.

(2) Any corrective measure taken by the Authority under paragraph (1) shall be notified by the Authority to the sponsor or investigator and shall specify the date on which the measure shall take effect.

(3) Before the Authority takes a measure under Article 77(1) of the Clinical Trials Regulation, it shall, except where immediate action is required, ask the sponsor or the investigator for their opinion, which opinion shall be delivered within 7 days.

(4) When considering whether the requirements of the Clinical Trials Regulation continue to be met, the Authority may consult with—

- (a) the National Office, or
- (b) the nominated ethics committee, or
- (c) other Member States concerned,

before taking any of the measures referred to in Article 77(1) of the Clinical Trials Regulation.

(5) Where a measure is taken by the Authority under Article 77(1) of the Clinical Trials Regulation and paragraph (1) of this Regulation, the Authority shall immediately inform all Member States concerned through the EU portal, in accordance with Article 77(3) of the Clinical Trials Regulation.

PART 7 SAFETY REPORTING

25. For clinical trials in the State—

(1) investigators and sponsors shall comply with the reporting obligations to which they are subject under Articles 41, 42, and 43 of the Clinical Trials Regulation,

(2) the Authority may, by way of notification, require the sponsor to send it the records referred to in Article 41(3) of the Clinical Trials Regulation, or copies thereof.

26. For the purposes of Article 44(2) and (3) of the Clinical Trials Regulation, the Authority—

(1) shall cooperate with other Member States concerned in assessing the information reported under Articles 42 and 43 of the Clinical Trials Regulation, and

(2) may consult with the National Office or the nominated ethics committee in the performance of its obligations under paragraph (1).

27. Without prejudice to the obligations on safety reporting under Chapter VII of the Clinical Trials Regulation, the sponsor shall maintain records of all adverse events and serious adverse events relating to a clinical trial which are reported by the investigators for that trial.

PART 8

MANUFACTURING AND IMPORTATION OF MEDICINAL PRODUCTS USED IN CLINICAL TRIALS

28. In accordance with Article 61(1) of the Clinical Trials Regulation, the manufacturing and importation of investigational medicinal products shall be subject to the holding of a manufacturer's authorisation.

Exemptions, Register of Exemptions

29. (1) For the purposes of Article 61(5) of the Clinical Trials Regulation, setting out the conditions on which an exemption to the holding of an authorisation may apply—

(a) “pharmacists” means “registered pharmacist” as defined in Regulation 3(1) of these Regulations,

(b) “other persons legally authorised in the Member State concerned” means a registered medical practitioner, or a registered dentist, as defined in Regulation 3(1) of these Regulations, and

(c) a “clinic” includes a retail pharmacy business as defined in the Pharmacy Act 2007 (No. 20 of 2007).

30. (1) For the purposes of ensuring safety and reliability and robustness of the data generated in the clinical trial as required by Article 61(6) of the Clinical Trials Regulation, the Authority—

- (a) shall maintain a register of processes specified in Article 61(5) of the Clinical Trials Regulation that are undertaken in hospitals, clinics and health centres that are exempt from the requirements of Article 61(1) of the Clinical Trials Regulation, defined as “Register of Exemptions” in Regulation 3(1), and
- (b) the Minister may publish guidelines prescribing further appropriate and proportionate requirements as may be required to ensure the objectives of Article 61(6) of the Clinical Trials Regulation are met.

31. (1) Subject to paragraph (2), processes specified in Article 61(5) of the Clinical Trials Regulation shall not be carried out unless they have been included on the Register of Exemptions.

(2) Notwithstanding paragraph (1), a process that has not been included on the register specified in Regulation 30, may be carried out if—

- (a) the related clinical trial had commenced prior to 31 January 2022 and is being conducted under Directive 2001/20/EC, or
- (b) the process relates to a clinical trial conducted under the Clinical Trials Regulation whereby an application to be added to the Register of Exemptions has been submitted to the Authority pursuant to Regulation 32 by 31st of January 2023.

32. (1) An application for entry on to the register shall be—

- (a) made in writing, in accordance with any form and manner as the Authority at its discretion may require,
- (b) signed by or on behalf of the applicant, whether in ink or by means of electronic signature,
- (c) accompanied by any fee which may be payable in connection with the application,
- (d) subject to Regulation 31, be submitted prior to the intended commencement of the activity.

(2) The applicant shall notify the Authority without delay of any changes to the details of the registered process.

33. Following the receipt of an application for entry on the Register of Exemptions, the Authority may carry out an inspection of the process, as determined by risk assessment.

34. The Authority may not include a process on the Register of Exemptions where—

- (a) conditions for entry on to the register are not satisfied,
- (b) the information submitted is false or misleading.

35. The Authority may withdraw a registered process from the Register of Exemptions where—

- (a) it does not comply with these Regulations or a condition of entry on to the Register of Exemptions,
- (b) the applicant requests the withdrawal of the process,
- (c) it transpires that the information submitted in the application for entry to the Register of Exemptions is false or misleading.

Application for manufacturer's authorisation

36. (1) An application for the grant of a manufacturer's authorisation under Article 61 of the Clinical Trials Regulation shall be—

- (a) made in writing to the Authority,
- (b) signed by or on behalf of the applicant, whether in ink or by means of an electronic signature, and
- (c) accompanied by—
 - (i) a written undertaking that in the event of the authorisation being granted, the applicant will ensure fulfilment of the obligations arising by virtue of the terms and conditions of the authorisation, and
 - (ii) any fee which may be payable in connection with that application.

37. (1) Subject to the provisions of this Regulation, the Authority shall consider a valid application for a manufacturer's authorisation and grant or refuse to grant same within a period not exceeding 90 days from the date the application is received.

(2) Following receipt of an application, the Authority shall, by means of inspection or otherwise, confirm the accuracy of the particulars provided in the application and may give a notice in writing to the applicant requesting him or her to provide further information relating to the said particulars.

(3) Where the Authority gives a notice pursuant to paragraph (2), the period specified in paragraph (1) shall be suspended from the date the notice is given and shall recommence only on receipt of the information requested.

(4) The expiry of the period of 90 days referred to in paragraph (1) shall not confer any rights on the applicant, and in particular shall not—

- (a) confer a default or tacit manufacturer's authorisation on an applicant, or
- (b) be taken to imply that a manufacturer's authorisation has been granted or will be granted.

Grant or refusal of manufacturer's authorisation

38. (1) The Authority shall not grant a manufacturer's authorisation unless it is satisfied that—

- (a) the particulars supplied pursuant to Regulation 36 are accurate,
- (b) the applicant has—
 - (i) complied with the requirements of Regulation 36, and of Article 61 of the Clinical Trials Regulation, and
 - (ii) provided any additional information to the Authority as may have been required under Regulation 37.

(2) Subject to paragraph (1), the Authority may—

- (a) grant a manufacturer's authorisation in respect of any or all of—
 - (i) the types and pharmaceutical forms of the investigational medicinal product manufactured or imported,
 - (ii) the premises, and
 - (iii) the manufacturing or importation operations specified in the application ,
- (b) grant a manufacturer's authorisation in accordance with the application, but subject to the carrying out of certain obligations by the authorisation holder,
- (c) grant a manufacturer's authorisation otherwise than in accordance with the application, or
- (d) refuse to grant a manufacturer's authorisation.

(3) The provisions of Schedule III shall have effect where the Authority proposes to—

- (a) grant a manufacturer's authorisation in accordance with the application, but subject to the carrying out of certain obligations by the authorisation holder,
- (b) grant a manufacturer's authorisation otherwise than in accordance with the application, or
- (c) refuse to grant a manufacturer's authorisation.

(4) Where the Authority grants or refuses to grant an Authorisation in accordance with paragraph (2), it shall give the applicant a notice in writing stating in detail the reasons on which its decision is based.

(5) The Authority shall enter information in the EudraGMDP database in relation to all manufacturer's authorisations granted.

Effect of manufacturer's authorisation

39. (1) A manufacturer's authorisation shall apply and have effect only in relation to—

- (a) the types and pharmaceutical forms of investigational medicinal products manufactured or imported,

- (b) the manufacturing or importation operations, and
- (c) the premises,

specified in the application made pursuant to Regulation 36 and in respect of which the authorisation has been granted.

Obligations of manufacturers of investigational medicinal products

40. (1) Subject to Article 63 of the Clinical Trials Regulation and the provisions of these Regulations, an authorisation holder shall not—

- (a) manufacture for supply in the EEA, or for export, any investigational medicinal product except in accordance with the requirements set down in Schedule III and with the principles and guidelines of good manufacturing practice set down in Commission Delegated Regulation (EU) 2017/1569 supplementing the Clinical Trials Regulation, or
- (b) import any investigational medicinal products except in accordance with the requirements set down in Schedule IV, and with the principles and guidelines of good manufacturing practice set down in Commission Delegated Regulation (EU) 2017/1569 supplementing the Clinical Trials Regulation.

(2) An authorisation holder shall comply with the obligations set down in Schedule IV, as appropriate, and any further conditions or obligations as may be imposed in the authorisation.

Variation of manufacturer's authorisation

41. (1) The Authority may vary a manufacturer's authorisation, whether on the application of the authorisation holder or otherwise.

(2) Subject to the provisions of this Regulation, if the authorisation holder makes a valid application to vary any details in respect of the manufacturer's authorisation which has been granted, the Authority shall consider the application and may vary or refuse to vary the authorisation—

- (a) within a period not exceeding 30 days from the date the application is received if an inspection of the premises is not required, or
- (b) within a period not exceeding 90 days from the date the application is received if the Authority deems it necessary to conduct an inspection of any premises to which the variation relates.

(3) Following receipt of a valid application to vary a manufacturer's authorisation, the Authority may give a notice in writing to the applicant requesting him or her to provide further information relating to the contents of the application or any particulars relevant to the application.

(4) Where the Authority gives a notice pursuant to paragraph (3), and a period specified in paragraph (2) applies, that period shall be suspended from the

date the notice is given and shall recommence only on receipt of the information requested.

(5) The Authority may vary a manufacturer's authorisation where it considers it necessary to do so for the purpose of securing compliance with the Clinical Trials Regulation, and may make a manufacturer's authorisation conditional on the carrying out of certain obligations.

42. (1) The provisions of Schedule III shall have effect where the Authority—

- (a) proposes to vary a manufacturer's authorisation, otherwise than in accordance with a valid application by the authorisation holder,
- (b) proposes to make a manufacturer's authorisation conditional on the carrying out of certain obligations by the authorisation holder, or
- (c) proposes to refuse to vary a manufacturer's authorisation, after consideration of the application of the holder.

(2) Where the Authority—

- (a) varies a manufacturer's authorisation, otherwise than in accordance with the valid application by the authorisation holder, or
- (b) makes a manufacturer's authorisation conditional on the carrying out of certain obligations by the authorisation holder, or
- (c) after consideration of the application of the holder, refuses to vary a manufacturer's authorisation,

the Authority shall notify the holder of that authorisation in writing, stating in detail the reasons on which its decision is based.

(3) In this Regulation, "valid application" means an application—

- (a) made to the Authority in writing and signed by or on behalf of the applicant, whether in ink or by means of an electronic signature,
- (b) specifying the variation requested by the applicant,
- (c) accompanied by—
 - (i) such particulars and supporting documentation as are necessary to enable the Authority to consider the application, and
 - (ii) any fee which may be payable in connection with that application.

Suspension and revocation of manufacturer's authorisation

43. (1) The Authority may by a notice in writing to the authorisation holder, forthwith or from a date specified in the notice, suspend the authorisation for

such period as the Authority may determine, or revoke the authorisation, on one or more of the following grounds—

- (a) the holder is not carrying out or has indicated by a notice in writing that he or she is no longer to carry out, the manufacturing or importation operations to which the authorisation relates,
- (b) the matters specified in the application in accordance with Regulation 36 were false or incomplete in a material particular,
- (c) a material change of circumstances has occurred in relation to any of those matters or particulars,
- (d) the authorisation holder has failed to any material extent to comply with his or her obligations under Regulation 40,
- (e) the holder has manufactured or imported investigational medicinal products otherwise than in accordance with the terms of the authorisation,
- (f) the authorisation holder does not have the staff, premises, equipment or facilities necessary for carrying out properly the handling, storage, or distribution activities to which the authorisation relates, and
- (g) the authorisation holder has failed to carry out an obligation imposed by the Authority pursuant to Regulation 38(2)(b) or Regulation 42(2)(b).

(2) The suspension or revocation of a manufacturer's authorisation under this Regulation may be—

- (a) total, or
- (b) limited to—
 - (i) certain manufacturing or importation operations concerning medicinal products, or
 - (ii) particular premises or particular parts of any premises described in the manufacturer's authorisation.

(3) The provisions of Schedule III shall have effect where the Authority proposes to suspend or revoke a manufacturer's authorisation in accordance with this Regulation.

(4) Where the Authority suspends or revokes a manufacturer's authorisation in accordance with this Regulation, it shall notify the authorisation holder in writing, stating in detail the reasons on which its decision to suspend or revoke the authorisation is based.

PART 9
FEES

44. (1) In accordance with Article 86 of the Clinical Trials Regulation, the Authority may,

- (a) without prejudice to subparagraph (b), charge a fee, or fees, to the sponsor for:
 - (i) the assessment of clinical trial applications under Chapter II of the Clinical Trials Regulation and Regulations 8 and 9 of these Regulations, and
 - (ii) the assessment of applications for substantial modifications under Chapter III of the Clinical Trials Regulation and Regulation 12 of these Regulations;
 - (iii) consideration of an appeal submitted in accordance with Part 10 of these Regulations and Part 5 of S.I. No. 41 of 2022;
 - (iv) the review of safety reports submitted by sponsors;
 - (v) the inspection of a clinical trial site, or of a sponsor site, or of a site of any other entity involved in the conduct of a clinical trial.
- (b) charge a reduced fee, or fees, to non-commercial sponsors, for the activities under paragraph (1)(a)(i) or (ii).

(2) The amount of the fee, or fees, under paragraph (1)(a) and (b) shall be—

- (a) reviewed on an annual basis by the Authority and the National Office and approved by the Minister, and
- (b) published on the websites of the Authority and the National Office.

(3) The fees under paragraph (1)(a) and (b) shall be—

- (a) payable immediately upon submission of a clinical trial application through the EU portal in accordance with Article 5 and Article 14 of the Clinical Trials Regulation;
- (b) where applicable, payable immediately upon submission of a substantial modification application through the EU portal in accordance with Article 16 of the Clinical Trials Regulation;
- (c) non-refundable once the application for a clinical trial application or substantial modification application has been validated in accordance with Article 5, Article 17 or Article 20 of the Clinical Trials Regulation, as appropriate.

(4) The Authority shall remit a regular payment to the National Office in respect of the ethical review of applications for clinical trials and substantial modifications.

- (5) The Authority may charge fees in relation to an application for the grant or variation of a manufacturer's authorisation and inspection of a manufacturing site.
- (6) The Authority may charge fees in relation to applications to the Register of Exemptions, and in relation to the inspection of manufacturers and processes under that Register.

PART 10

APPEALS

45. (1) A sponsor may, within the time limit specified under paragraph (2), give notice to the Authority of his or her wish to submit an appeal in respect of a refusal to—

- (a) authorise a clinical trial pursuant to Article 8(4) of the Clinical Trials Regulation, and under these Regulations,
- (b) authorise a clinical trial pursuant to Article 14(10) of the Clinical Trials Regulation, and under these Regulations, or
- (c) authorise a substantial modification pursuant to Articles 19(2), 20(7) or 23(4) of the Clinical Trials Regulation, and under these Regulations.

(2) Any appeal shall be submitted to the Authority within 28 days of receipt of a refusal specified in paragraph (1).

(3) The provisions of Schedule I, and of Part 5 of S.I. No. 41 of 2022, shall apply to the submission and processing of an appeal submitted by a sponsor under paragraph (1).

PART 11

LANGUAGE

Application dossier

46. For clinical trials to be conducted in the State and for the purposes of Article 26 of the Clinical Trials Regulation, the

- (1) application dossier described under Article 25 of the Clinical Trials Regulation, and
- (2) any documentation addressed to subjects,

shall be in English.

Labelling

47. (1) For the purposes of Article 69 of the Clinical Trials Regulation and without prejudice to paragraph (2), the language of the information required to

appear on the label of an authorised or unauthorised investigational medicinal product or auxiliary medicinal product used in a clinical trial shall be English.

(2) Paragraph (1) shall not preclude the information specified therein also appearing on the label in one or more languages, other than English.

PART 12

OFFENCES, PENALTIES, AND ENFORCEMENT

Offences

48. (1) A person who—
 - (a) commences a clinical trial in the State without—
 - (i) notification of authorisation, in accordance with Regulation 10, or
 - (ii) having in place a scheme to provide compensation for any damage suffered by a subject resulting from a clinical trial in accordance with Regulation 17,
 - (b) commences a substantial modification to a clinical trial without notification of authorisation in accordance with Regulation 13,
 - (c) conducts a clinical trial, other than in accordance with the requirements of Regulation 14,
 - (d) performs the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), other than in accordance with the requirements of Regulation 14,
 - (e) performs the functions of the investigator of a clinical trial, other than in accordance with the requirements of Regulation 14,
 - (f) charges a fee to a subject of a clinical trial other than in accordance with Regulation 16,
 - (g) fails to maintain a trial master file in accordance with the requirements of Article 57 of the Clinical Trials Regulation and Regulation 20,
 - (h) fails to make available to the Authority a trial master file in accordance with the time periods set out in Regulation 20(2),
 - (i) fails to meet their obligations in relation to archiving under Article 58 of the Clinical Trials Regulation and Regulation 21(1),
 - (j) fails to retain the medical files of clinical trial subjects in accordance with Regulation 21(2),
 - (k) fails to pay a fee due under Regulation 44,
 - (l) labels, sells, or supplies a medicinal product or auxiliary medicinal product other than in accordance with Regulation 47,
 - (m) fails to comply with a notice of suspension or termination served under Regulation 24 or 43, unless same has been withdrawn or revoked by the Authority,

- (n) in—
 - (i) an application for an ethics committee opinion,
 - (ii) an application for authorisation under Chapter II of the Clinical Trials Regulation to conduct a clinical trial in the State,
 - (iii) an application for a substantial modification to a previously authorised clinical trial under Chapter III of the Clinical Trials Regulation,

provides to the Authority, the nominated ethics committee, or the National Office any relevant information which is false or misleading in a material particular,
- (o) in—
 - (i) the conduct of a clinical trial authorised in accordance with these Regulations,
 - (ii) the sponsorship of such a clinical trial,
 - (iii) the performance of the functions of a sponsor, when acting under arrangements made with the sponsor of such a clinical trial,
 - (iv) the performance of the duties of a qualified person in accordance with Article 61 of the Clinical Trials Regulation,
 - (v) the holding of a manufacturing authorisation,
 - (vi) securing or maintaining a listing on the Register of Exemptions

provides to the Authority, the nominated ethics committee or the National Office any relevant information which is false or misleading in a material particular,
- (p) wilfully obstructs or interferes with the exercise of a power by an authorised officer pursuant to Regulation 54,
- (q) without reasonable excuse, fails to comply with any request made by an authorised officer under Regulation 54,
- (r) fails to comply with the provisions laid down in the Clinical Trials Regulations on the submission of information intended to be made publicly available to the EU database,
- (s) fails to comply with safety reporting requirements as laid down in Articles 41, 42 and 43 of the Clinical Trials Regulation,
- (t) fails to provide records requested by the Authority in accordance with Regulation 25(2),
- (u) fails to meet the requirements of Article 54 of the Clinical Trials Regulation in relation to Urgent Safety measures,
- (v) fails to establish a legal representative in accordance with Article 74(1) of the Clinical Trials Regulation when required,

- (w) fails to meet the requirements of the Clinical Trials Regulation, or of Part 4 of these Regulations, in relation to the protection of clinical trial subjects and informed consent,
- (x) fails to comply with the requirements for the manufacture and import of investigational medicinal products and auxiliary medicinal products in accordance with Regulation 40,
- (y) sells or supplies an investigational medicinal product for the purposes of a clinical trial knowing or having reasonable cause to suspect that it was manufactured, labelled, packaged or imported in contravention of Regulation 40,
- (z) otherwise than for the purpose of performing or exercising a duty or power imposed or conferred by or under these Regulations, is in possession of an investigational medicinal product knowing or having reasonable cause to suspect that it was imported in contravention of Regulation 40,
- (aa) fails to comply with the requirements for notifications and submissions laid down in Article 36, 37, and 38 of the Clinical Trials Regulation,

is guilty of an offence.

(2) The offences listed in paragraph (1) also apply to a legal representative of a sponsor responsible for ensuring compliance with the sponsor's obligations in the State pursuant to Article 74(1) of the Clinical Trials Regulation.

Penalties

49. (1) A person guilty of an offence under these Regulations shall be liable on summary conviction to a fine not exceeding €3,000, or to imprisonment for a term not exceeding six months, or both.

(2) A person guilty of an offence under these Regulations shall be liable on conviction on indictment to a fine not exceeding €300,000, or to imprisonment for a term not exceeding 3 years, or both.

Body corporate

50. Where an offence under these Regulations is committed by a body corporate and is proved to have been so committed with the consent, connivance or approval of or to have been attributable to the wilful neglect on the part of any person, being a director, manager, qualified person, secretary or other officer of the body corporate or a person who was purporting to act in any such capacity, that person as well as the body corporate shall be guilty of an offence and shall be liable to be proceeded against and punished as if he or she was guilty of the first mentioned offence.

Separate contraventions

51. For the purposes of these Regulations, every contravention of a provision of these Regulations shall be deemed a separate contravention and every contravention of a paragraph or a subparagraph shall also be deemed to be a

separate contravention and shall carry the same penalty as for a single contravention of any such provision.

Infringement notices

52. (1) If the Authority has objective grounds for considering that any person has contravened any provision of these Regulations, it may serve upon that person a notice in writing (in these Regulations referred to as an “*infringement notice*”) –

- (a) informing him or her of the Authority’s grounds for considering that the person has contravened one or more of those provisions,
- (b) specifying the relevant provision of these Regulations,
- (c) specifying the measures which the person must take in order to ensure that the contravention does not continue or, as the case may be, does not recur,
- (d) requiring the person to take those measures, within such period as may be specified in the notice,
- (e) warning the person that unless the requirements of subparagraph (d) are met, further action may be taken in respect of the contravention.

(2) An infringement notice may include directions as to the measures to be taken by the person on whom the notice is served to ensure that the contravention does not continue or, as the case may be, does not recur, including the different ways of securing compliance.

(3) If the Authority serves an infringement notice in accordance with paragraph (1), it shall forthwith inform the nominated ethics committee.

Defence of due diligence

53. In any proceedings for an offence under any of the preceding provisions of these Regulations, it shall be a good defence for a person charged to show that he or she reasonably believed that the said provisions had been complied with.

Enforcement generally

54. (1) These Regulations and the provisions of the Clinical Trials Regulation to which they refer, shall be enforced by the Authority.

(2) In carrying out its compliance and enforcement role under the Clinical Trials Regulation and these Regulations, the Authority shall ensure that confidentiality is respected by authorised officers and other experts engaged in good clinical practice inspections and, with regard to personal data, that the requirements of the General Data Protection Regulation and the Data Protection Acts 1988 to 2018 are respected.

Appointment of authorised officers

55. (1) For the purposes of ensuring compliance with the Clinical Trials Regulation and these Regulations, the Chief Executive of the Authority may

appoint such and so many persons as he or she thinks fit to be authorised officers, and each authorised officer shall be furnished with a warrant of appointment.

(2) An authorised officer shall, when performing a function imposed on an authorised officer under these Regulations, produce his or her warrant for inspection if requested to do so by a person affected by the performance of that function.

Functions of authorised officers

56. (1) An authorised officer shall carry out such inspections as are necessary to enforce these Regulations and the Clinical Trials Regulation.

(2) Without prejudice to paragraph (1), good clinical practice inspections may be carried out on any of the following occasions—

- (a) before, during or after the conduct of clinical trials;
- (b) as part of the verification of applications for a manufacturing or marketing authorisation;
- (c) as a follow-up to the granting of authorisation;
- (d) where services are provided for the support of clinical trials.

(3) Subject to paragraphs (4) and (5) an authorised officer may, for the purpose of ensuring that these Regulations are being complied with, carry out all or any of the following acts—

- (a) at all reasonable times, enter (if necessary, by the use of reasonable force) and search a premises of any class or description,
- (b) inspect any substance or product which is stored, or offered or kept for sale or supply at such premises,
- (c) require the production of, inspect and, if he or she thinks fit, take copies of any book, invoice, order, record, register, or other document or of any entry in any such book, invoice, order, record, register, or other document at such premises,
- (d) inspect and copy or extract information from any data (including personal data) within the meaning of the General Data Protection Regulation and the Data Protection Acts 1988 to 2018,
- (e) take (with or without payment) samples of any investigational medicinal product or substance stored, or offered or kept for sale or supply at such premises for test, examination or analysis,
- (f) detain and if necessary seize any investigational medicinal product, substance or article,
- (g) take any document which he or she has reasonable cause to believe to be a document which may be required as evidence in proceedings under these Regulations,
- (h) inspect and take copies, or samples of, labels used, or intended to be used on an investigational medicinal product,
- (i) require any person carrying on, or who has carried on, an activity to which these Regulations relate, or any person currently or previously employed in connection with such an activity, to give

to the authorised officer such information as the authorised officer may reasonably require for the purposes of these Regulations,

- (j) take photographs of premises and equipment,
- (k) contact the subject of a clinical trial directly, in accordance with Article 10(6) of Regulation (EU) 2017/556, and
- (l) ask any representative or member of staff of the inspected entity and any party involved in the clinical trial for explanations relating to the subject matter and purpose of the inspection and record the answer.

(4) An authorised officer shall not, other than with the consent of the occupier, enter a private dwelling unless he or she has obtained a warrant from the District Court under paragraph (9) authorising such entry.

(5) Any expert who accompanies an authorised officer may:

- (a) ask any representative or member of staff of the inspected entity and any party involved in the clinical trial for explanations relating to the subject matter and purpose of the inspection and record the answer,
- (b) review, record, and extract information from any data (including personal data) within the meaning of the General Data Protection Regulation and the Data Protection Acts 1988 to 2018.

(6) When exercising a power under this Regulation, an authorised officer may, subject to any warrant under paragraph (9), be accompanied by such number of—

- (a) other authorised officers,
- (b) inspectors from the competent authority of another Member State,
- (c) persons with expertise relevant to the aspects being examined, or
- (d) members of An Garda Síochána or Customs and Excise Officers,

as he or she considers appropriate, in the circumstances of the case.

(7) An authorised officer, for the purpose of exercising any of the powers conferred on him or her by paragraph (3), may require any other person, having authority to do so, to break open any container or package or to permit him or her to do so.

(8) Where an authorised officer seizes any medicinal product, substance, article or document in the exercise of a power conferred on him or her by paragraph (3), he or she shall inform the person from whom it is seized.

(9) If a judge of the District Court is satisfied, on the sworn information of an authorised officer, that there are reasonable grounds to authorise entry into any premises referred to in paragraph (4), the judge may issue a warrant authorising such an authorised officer, accompanied, if appropriate, by other authorised officers or by a member or members of the Garda Síochána, or both, at any time or times within one month from the date of issue of the warrant, on production of the warrant if requested, to enter those premises or part thereof and to exercise any of the powers conferred on such an authorised officer under this Regulation.

(10) A person shall not wilfully obstruct or interfere with the exercise of a power by an authorised officer pursuant to this Regulation.

(11) A person shall not, without reasonable excuse, fail to comply with any request made by an authorised officer under this Regulation.

(12) Any material taken away by an authorised officer under this Regulation may be retained by him or her for use in evidence in any proceedings.

Prosecution of offences

57. Proceedings in relation to a summary offence under these Regulations may be brought and prosecuted by the Authority.

PART 13

JOINT CONTROLLERSHIP ARRANGEMENT

58. The Authority and the National Office shall be the State's joint controllers for the purpose of processing personal data captured in the EU portal, and shall be identified as such in Annex I of the Joint Controllership Arrangement.

PART 14

REVOCATIONS

59. Subject to Regulations 61 and 62, the following are revoked:

- (a) European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 (S.I. No. 190 of 2004);
- (b) European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment) Regulations 2004 (S.I. No. 878 of 2004);
- (c) European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment No. 2) Regulations 2006 (S.I. No. 374 of 2006);
- (d) European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment) Regulations 2009 (S.I. No. 1 of 2009).
- (e) European Union (Clinical Trials on Medicinal Products for Human Use) Regulations 2022 (S.I. No. 40 of 2022).

PART 15

ENTRY INTO FORCE AND TRANSITIONAL ARRANGEMENTS

60. These Regulations will come into operation immediately and shall only apply to clinical trial applications submitted under the Clinical Trials Regulation.

61. Notwithstanding the revocation, by Regulation 59 of these Regulations and Regulation 37 of S.I. No. 40 of 2022, of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 -

- (a) those Regulations shall continue to apply until the 30th day of January 2025
 - (i) in respect of an application submitted in accordance with those Regulations before the 31st day of January 2022, and
 - (ii) in respect of an application made on or before the 31st day of January 2023, where the sponsor opted to make the application in accordance with those Regulations, and
- (b) a sponsor of a clinical trial that received a favourable opinion from an ethics committee recognised by the Minister in accordance with Part 2 of those Regulations and, in relation to which trial the Authority granted an authorisation, shall continue to comply with his or her reporting obligations under those Regulations until the 31st day of January 2025.

62. (1) Subject to paragraph (2), any

- (a) manufacturer's licence granted under Regulation 33 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 (S.I. 190 of 2004), or
- (b) manufacturer's authorisation granted under Regulation 8 of the Medicinal Products (Control of Manufacture) Regulations 2007 to 2019 in respect of investigational medicinal products,

shall continue to be in force as if granted under these Regulations.

(2) An application made in respect of the grant or variation of a manufacturer's authorisation under the Medicinal Products (Control of Manufacture) Regulations 2007 to 2019, and which has not been determined prior to the date of coming into force of these Regulations, shall be considered as if it were an application made under Regulation 36 of these Regulations. In all cases, where the information provided in such applications is not sufficient, the Authority may require that the applicant shall update his or her application to conform to the provisions of Regulation 36.

(3) Persons referred to in Regulation 29 who had commenced their activity before 31 January 2022 shall submit the application to the Authority to be listed on the Register of Exemptions by 31st March 2022.

63. Subject to Regulations 61 and 62 of these Regulations, any action taken in reliance upon S.I. No. 40 of 2022 prior to the commencement of these Regulations and after the commencement of S.I. No. 40 of 2022 shall be deemed to be regulated by these Regulations.



GIVEN under my Official Seal,
2 March, 2022.

STEPHEN DONNELLY,
Minister for Health.

SCHEDULE I

PROCEDURAL PROVISIONS RELATING TO DECISIONS TO REFUSE A REQUEST FOR CLINICAL TRIAL AUTHORISATION OR TO REFUSE A SUBSTANTIAL MODIFICATION TO AN AUTHORISED CLINICAL TRIAL

1. Where the Authority is notified of the sponsor's wish to appeal a decision in accordance with Regulation 45, the Authority shall determine if the appeal relates to the conclusion on the Part I or Part II assessment, or both, and
 - (1)in the case of an appeal relating solely to the conclusion on Part I of the assessment report, process the appeal in accordance with point 2; or
 - (2)in the case of an appeal relating solely to the conclusion on Part II of the assessment report, refer the appeal to the National Office for processing in accordance with point 3; or
 - (3)in the case of an appeal relating to the conclusions of both Part I and Part II of the assessment reports, process the Part I aspects in accordance with point 2, and refer the appeal to the National Office for processing of the Part II aspects in accordance with point 3;

and shall notify the sponsor how the appeal shall be heard.
2. (1)The Authority shall afford an opportunity for the sponsor to make representations to the Advisory Committee for Human Medicines.
 - (2)The Advisory Committee may seek advice on ethical aspects of the appeal from the National Office and/or the nominated ethics committee, if relevant.
 - (3)After considering the representations, the Advisory Committee shall report its findings and advice, and the reasons for its advice, to the Authority.
 - (4)The Authority shall, after considering the report of the Advisory Committee –

- (a) confirm the administrative single decision not to accept the request for authorisation of a clinical trial application or substantial modification application,
- or
- (b) accept the request for authorisation of a clinical trial application or substantial modification application.
3. (1) The National Office shall establish an appeals panel, and that panel shall hear the appeal, in accordance with Regulations 25 and 26 of S.I. No. 41 of 2022.
- (2) The National Office shall notify the Authority of the outcome of the appeal no later than 45 days after the appeal was referred to it pursuant to point (1).
- (3) The National Office shall, after considering the report of the appeals panel—
- (a) confirm the administrative single decision not to accept the request for authorisation of a clinical trial application or substantial modification application, or
 - (b) accept the request for authorisation of a clinical trial application or substantial modification application.
4. (1) In the case of an appeal to which point 1(3) applies, the Authority shall, after considering the report of the Advisory Committee pursuant to point 2(3), and the report of the appeals panel committee pursuant to point 3(2),
- (a) confirm the administrative single decision not to accept the request for authorisation of a clinical trial application or substantial modification application; or
 - (b) accept the request for authorisation of a clinical trial application or substantial modification application.
- (2) In the case of an appeal to which point 1(3) applies, if the appeal on one aspect of the assessment report is not successful, the appeal shall not be upheld.
5. The Authority shall notify the sponsor of the outcome of the appeal no later than 52 days after receipt of the appeal.

SCHEDULE II

PARTICULARS THAT MUST ACCOMPANY AN APPLICATION FOR A MANUFACTURER'S AUTHORISATION

1. The name and address of the natural or legal person proposed to be the authorisation holder.
2. The address of each of the premises where the manufacturing or importation of the investigational medicinal products to which the application relates, including any testing and controls associated with such activities, that are to be carried out.
3. The name of any organisation and address of the associated premises to which the proposed authorisation holder proposes to outsource manufacturing, testing activities concerning the investigational medicinal product.
4. (1) A site master file covering the premises, manufacturing, importation and quality control operations specified in the application form.
(2) A site master file shall be prepared in accordance with the guidance published by the European Commission in Part III of the EU Good Manufacturing Practice guidelines.
5. (1) The name, qualifications and experience of the qualified person who shall carry out the duties referred to in Article 62 of the Clinical Trials Regulation.
(2) In the case of an authorisation relating to manufacturing activities, the name, qualification and experience of the production manager other person whose duty it shall be to supervise the production operations at each of the premises referred to in point 2.
(3) In the case of an authorisation relating to manufacturing activities, that name and degrees, diplomas or other qualifications and experience of the person to be in charge of quality control over all the premises referred to in point 2.
6. In this Schedule, the reference to investigational medicinal products includes blood products, immunological products, cell therapy products, gene therapy products, biotechnology products, human or animal extracted products, herbal products, homeopathic products, radiopharmaceutical products and products containing chemical agents.

SCHEDULE III

**PROCEDURAL PROVISIONS RELATING TO PROPOSALS TO GRANT
SUBJECT TO THE CARRYING OUT OF CERTAIN OBLIGATIONS,
PROPOSALS TO GRANT OTHERWISE THAN IN ACCORDANCE WITH
THE APPLICATION, PROPOSALS TO REFUSE TO GRANT OR VARY,
PROPOSALS TO MAKE THE AUTHORISATION CONDITIONAL ON
THE CARRYING OUT OF CERTAIN OBLIGATIONS, AND PROPOSALS
TO SUSPEND, VARY OR REVOKE A MANUFACTURER'S
AUTHORISATION**

1. In this Schedule—

‘authorisation’ means a manufacturer’s authorisation, and

‘time allowed’ means the period of 28 days or such extended period as the Authority may in any particular case allow.

2. Subject to point 6, if the Authority proposes—

(1) not to grant an authorisation,

(2) to grant an authorisation subject to the carrying out of certain obligations,

(3) to grant an authorisation other than in accordance with the application,

(4) to revoke, vary or suspend an authorisation,

(5) not to vary an authorisation on the holder’s application to vary, or

(6) to make an authorisation conditional on the carrying out of certain obligations,

the Authority shall notify the applicant or authorisation holder accordingly.

3. Any notification given under point 2 shall include—

(1) a statement of the proposals of the Authority,

(2) a statement setting out in detail the reasons on which the said proposals are based, and

(3) a statement that the applicant or authorisation holder has the right to make representations to the Authority in response to the notification.

4. A person to whom notification has been given under point 2 may, within the time allowed after the notification was given, give notice to the Authority of his or her wish to do so, and make representations to the Authority with respect to the decision or proposal referred to in the notification.

5. The Authority shall, after considering the representations, decide whether to grant the authorisation, revoke, vary or suspend an authorisation or confirm or alter its decision, as the case may be.

6. (1) Point 2 shall not apply to the suspension of an authorisation where it appears to the Authority that, in the interests of safety, it is necessary to suspend the authorisation with immediate effect for a period not exceeding 3 months.
- (2) If, after the aforementioned suspension has taken effect, it appears to the Authority that the authorisation should be further suspended or revoked, the Authority shall proceed in accordance with the provisions of points 2 to 5.

SCHEDULE IV

REQUIREMENTS TO BE MET BY AN AUTHORISATION HOLDER MANUFACTURING OR IMPORTING INVESTIGATIONAL MEDICINAL PRODUCTS

1. The authorisation holder shall—
 - (1) comply with the requirements set out in the Commission Delegated Regulation 2017/1569,
 - (2) operate only within the scope and terms defined in the authorisation.
2. The authorisation holder shall at all times provide and maintain such staff, premises equipment and facilities as will enable the qualified person at his or her disposal pursuant to Article 61(2)(b) of the Clinical Trials Regulation to carry out the duties referred to in Article 62(1) of the Clinical Trials Regulation.
3. The authorisation holder shall give prior written notice to the Authority—
 - (1) of any changes he or she may wish to make to any details specified in the authorisation,
 - (2) where it is intended to introduce significant changes to the premises or activities to which the authorisation relates, including changes which introduce significant new risks that have to be managed.
4. The authorisation holder shall, where manufacture is carried out under the authorisation, keep an adequate sample of each batch and of each active constituent used in the manufacture of the investigational medicinal products to which the authorisation relates, for the period which ends one year after the labelled expiry date of the product, and shall furnish on request by the Authority a sufficient sample of each such batch for the purpose of any test, examination or analysis which may be requested by the Authority. The Authority will not be charged for any such samples.
5. The authorisation holder shall, where manufacture is carried out under the authorisation, ensure that any human blood or blood component imported into the State and used by him or her as a starting material or as a raw material in the manufacture of an investigational medicinal product shall meet the equivalent standards of quality and safety to those laid down in Commission Directive 2004/33/EC⁶.
6. The authorisation holder shall supply such information as may be requested by the Authority for the purposes of these Regulations about the manufactured or imported investigational medicinal products and about the operations being carried out under the authorisation.
7. The authorisation holder shall for the purpose of enabling the Authority to—

⁶ O.J. No. L 91, 30.3.2004, p. 25.

- (1) verify any statement contained in an application for a manufacturer's authorisation or clinical trial application, or
- (2) ascertain whether there are any grounds for suspending, revoking or amending any such authorisation,
- permit, and provide all necessary facilities to enable, authorised officers to enter and inspect his or her premises at any time and to take such samples or to take copies of any documents in relation to any such application or authorisation as may be required.
8. The authorisation holder shall from time to timer permit such inspection and make available such information as may be required to satisfy the Authority that the conditions of the authorisation are being complied with.
 9. Where the authorisation holder has been informed by the Authority that any part of a batch of an investigational medicinal product to which his or her authorisation relates has been found not to conform as regards strength, quality or purity with the specifications of the relevant investigational medicinal product he or she shall, if so directed by the Authority, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.
 10. Where the authorisation holder has been informed by the Authority that an investigational medicinal product to which his or her authorisation relates has been found to give rise to concerns in regard to its safety or efficacy, he or she shall, if so directed by the Authority, immediately withhold that investigational medicinal product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such investigational medicinal product already sold, supplied or exported.
 11. Where the authorisation holder has been informed by the Authority that any batch of an investigational medicinal product, or part thereof, to which his or her authorisation relates, has not been manufactured in accordance with the principles and guidelines of good manufacturing practice set out in the Commission Delegated Regulation 2017/1569, he or she shall, if so requested by the Authority, immediately withhold that investigational medicinal product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such investigational medicinal product already sold, supplied or exported.
 12. Where the authorisation holder decides for whatever reason to recall a particular batch of an investigational medicinal product manufactured or imported by him or her, or part thereof, he or she shall forthwith inform the Authority of the decision to recall and of the reason for such recall.
 13. Where the authorisation holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of a particular investigational medicinal product manufactured or imported by him or her, or of a batch or part of batch thereof, he or she shall consult with the Authority in relation to the action which may be considered appropriate in the circumstances.

14. (1) The authorisation holder, in the case of manufacture of an advanced therapy investigational medicinal product, shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the trial site where the product is used.
- (2) Where an authorisation holder manufactures an advanced therapy investigational medicinal product that contains human cells or tissues, he or she shall ensure that the traceability systems established in accordance with subparagraph 1 are complimentary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC⁷, and Articles 14 and 24 of Directive 2002/98/EC⁸.
- (3) The authorisation holder shall keep the data referred to in paragraph (1) for a minimum of 30 years after the expiry date of the product.
- (4) In the case of bankruptcy or liquidation of the authorisation holder who has manufactured an advanced therapy investigational medicinal product, and in the event that the manufacturer's authorisation is not transferred to another legal entity, the data referred to in paragraph (1) shall be transferred to the Authority.
- (5) In the event that the manufacturer's authorisation is suspended, revoked or withdrawn, the holder of the manufacturer's authorisation shall remain subject to the obligations laid down in paragraphs (1), (2) and (3).
- (6) Paragraphs (3) to (5) shall not apply to a holder of a manufacturer's authorisation where the holder of a marketing authorisation for the relevant advanced therapy investigational medicinal product is, by virtue of such marketing authorisation, responsible for the retention of such data.
15. The content of the site master file shall be kept up to date at all times. Each time the site master file is updated, a copy of the updated file shall be provided to the Authority.
16. The Authority may request the authorisation holder to confirm accuracy of details within the site master file.

⁷ O.J. No. L 102, 7.4.2004, p. 48.

⁸ O.J. No. L 33, 8.2.2003, p. 30.

EXPLANATORY NOTE

(This note is not part of the Instrument and does not purport to be a legal interpretation).

These Regulations give further effect to Regulation (EC) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use (“Clinical Trials Regulation”) which applied from the 31st of January 2022.

The Clinical Trials Regulation replaces and repeals Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The National Office and National Research Ethics Committees, have been defined in separate Regulations, the European Union Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022 (S.I. No. 41 of 2022).

These Regulations also revoke S.I. No. 40 of 2022, which was put in place as interim regulations to transpose those elements of the Clinical Trials Regulation which concerned Member State competences into Irish Law from the date of the application of the Clinical Trials Regulation. These regulations now replace S.I. No. 40 of 2022 as the Principal Regulations which give further effect to the Clinical Trials Regulation.

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