

Brussels, 8 September 2026
(OR. en)

12598/26

Interinstitutional File:
2025/0406 (COD)

LIMITE

SAN 630
PHARM 147
COMPET 1018
CODEC 1563
RECH 341
BIOTECH 93
ENV 1013
PI 101
FOOD 115
FEED 45
VETER 136
AGRI 631
AGRILEG 202
DENLEG 86

WORKING DOCUMENT

From:	Presidency
To:	Delegations
No. Cion doc.:	16945/25 + ADD 1
Subject:	Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health and amending Regulations (EC) No 178/2002, (EC) No 1394/2007, (EU) No 536/2014, (EU) 2019/6, (EU) 2024/795 and (EU) 2024/1938 (European Biotech Act) - First presidency compromise text

Delegations will find in Annex the first compromise text of Article 58: Amendments to Regulation (EU) No 536/2014, to be discussed at the meetings of the Working Party on Pharmaceuticals and Medical Devices on 16-17 September 2026.

The text is as it appears in the Biotech Act (2025/0406) incorporating all changes made by the IE Presidency. This document also contains changes made to recitals and annexes in the Biotech Act which relate to the CTR.

While Recitals 122 through 159 of the Biotech Act were examined, only recitals that have been amended to reflect changes made to the main text are included. The IE PRES will continue to review the recitals at each iteration and make changes as necessary.

Within the Annex, the Presidency has only included the sections that have been amended in the Commission text or in the Presidency compromise text.

Deletions are shown in ~~strike through~~, replacements and additions are shown in **bold underlined**.

Recitals

- (127) To accelerate and streamline the approval processes in multinational clinical trials it is necessary to give a stronger leading role to the reporting Member State and further strengthen the principles of mutual trust and reliance. **Rules related to the appointment of the reporting Member State are to be defined, with the Clinical Trials Coordination and Advisory Group providing recommendations on criteria for the selection of a reporting Member State. It is important that these provisions facilitate the selection of a reporting Member State with appropriate available expertise to take a leading role in the assessment of the clinical trial application.** The assessment by the reporting Member State, including of the ethical aspects of the trial, should serve as a reference for the other Member States concerned. Member States concerned should complement the assessment by the reporting Member State only when necessary, and be entitled to raise considerations from ethical, relevant national law or national standard of care perspectives. Strengthening reliance on the reporting Member State's assessment would reduce duplication of work and allow Member States and sponsors to allocate resources more effectively, while ensuring high level of protection of subjects and the robustness of data.

- (136) The experience gained during the Covid-19 pandemic has shown the need for the Union to swiftly take up measures to strengthen the development and access to crisis-relevant medicines, including to accelerate, simplify, and streamline the authorisation of multinational clinical trials relevant to prevent, treat or diagnose the disease caused by an emerging serious cross-border threat to health. Regulatory flexibility, including an accelerated authorisation procedure for clinical trials, is necessary to address and possibly contain an emerging health threat in a timely, efficient and coordinated manner. Therefore, it is appropriate to allow for an accelerated procedure for the authorisation of multinational clinical trials in situations where a public health emergency at Union level has been recognised in accordance with Article 23(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council⁵⁴, or in situations of an emerging serious cross-border threat to health that is likely to lead to the recognition of a public health emergency at Union level. This should also complement measures from the Regulation (EU) 2022/2372 of the Council⁵⁵ on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level.
- Member states may adopt accelerated timelines for clinical trials involving investigational medicinal products in the earliest stages of development with the aim of promoting earlier access to innovative therapies and to allow healthcare systems to accumulate implementation experience. Without prejudice to this Regulation, Member States remain solely responsible for their own national security. They are responsible for defending their essential state functions, including ensuring their territorial integrity and safeguarding national security. Member States should therefore also be able to adopt accelerated timelines for clinical trials related to biodefence or addressing a need related to the protection of national security and defence.**

(150) The processing of personal data under Regulation (EU) No 536/2014 should comply with the requirements for the protection of personal data, including genetic data and data concerning health, laid down in Regulations (EU) 2016/679⁵⁶ and (EU) 2018/1725⁵⁷ of the European Parliament and of the Council. It is appropriate to clarify that the basis for the processing of personal data in the context of clinical trials is laid down in Regulation (EU) No 536/2014, pursuant to Article 6(1), point (c), of Regulation (EU) 2016/679. The Agency should have access to personal data necessary to perform its tasks in the public interest or complying with legal obligations in accordance with Articles 40, 80 and 81 of Regulation (EU) No 536/2014. The Commission should have access to personal data necessary for it to perform its task in accordance with Articles 78, 79, 80, 81, of Regulation (EU) No 536/2014. **For the purposes of inspections carried out in accordance with Article 78, competent authorities may require access to source documents, including documents containing directly identifiable information, where and to the extent necessary to verify data integrity and to protect the rights, safety and wellbeing of participants. Such access may be exercised on site or, where duly justified, remotely, primarily for examination, analyse and verification purposes, under the control of the data controller and subject to appropriate technical and organisational safeguards. Inspectors are bound by statutory duties of professional secrecy and shall process any personal data accessed exclusively for inspection purposes and in accordance with applicable data protection requirements. Where copies or extracts of source documents are requested to remain with the competent authority, documents containing personal data should, as a general rule, be provided in a redacted or pseudonymised form. Only in justified exceptional cases (e.g. suspected fraud or serious irregularities), and where no less intrusive means are available, may limited directly identifiable elements exceptionally remain unredacted. In all cases, the scope and extent of access, copying, redaction or disclosure should be appropriate and proportionate to the inspection objective.**

- (151) **Regulation (EU) 2016/679 provides that, where the purposes and means of processing are determined by the Union, the controller or the specific criteria for its nomination may be provided by that law. For the purposes of legal clarity and legal certainty, it is appropriate to designate in this Regulation the site within which the investigator conducts a clinical trial as the controller, within the meaning of Regulation (EU) 2016/679, in respect of the processing activities carried out by the investigator for the conduct of the clinical trial. Similarly, it is appropriate to designate in this Regulation also the sponsor of the clinical trial as the controller within the meaning of Regulation (EU) 2016/679, in respect of the processing activities carried out by the sponsor for the conduct of the clinical trial, including processing activities necessary for the design, management, conduct and oversight of the clinical trial.**

~~In particular, Regulation (EU) No 536/2014 should be amended to require the processing of personal data by the sponsors and investigators where this is necessary to comply with the legal obligations imposed on them to ensure the safety and efficacy of medicinal products, when they request authorisation for and conduct clinical trials. This includes obligations to perform research activities in accordance with an authorised protocol, to perform safety reporting, and to perform archiving in accordance with Regulation (EU) No 536/2014.~~

The relevant information to be collected according to authorised protocol will contain personal data of the subjects, including genetic data or data concerning health.

Additionally, personal data may encompass identification details, such as sex and age, social insurance numbers and contact information. Moreover, sponsors may collect and process other data necessary for implementing the authorised protocol, such as the personal data of investigators. The categories of personal data to be collected and processed in the context of a specific clinical trial should be specified in the authorised protocol. Regulation (EU) No 536/2014 should be amended to establish specific safeguards for the processing of personal data, including genetic data or data concerning health, in compliance with Article 9(2), points (i) and (j), of Regulation (EU) 2016/679. For instance, it should require informed consent to participate in the clinical trial, as well as to maintain confidentiality of records and personal data of participants. The protocol should specify further appropriate safeguards such as specific technical and organisational measures that should be employed, including pseudonymisation, integrity and confidentiality controls, encryption and access restrictions. In addition, any clinical trial should be subject to ethical review.

- (153) Personal data which is collected and processed under each authorised protocol in accordance with Regulation (EU) No 536/2014 as amended by this Regulation may be further processed by the same controller for the purposes of other clinical trials, conducted in accordance with Regulation (EU) No 536/2014. Such data may include names, contact details **of the investigator**, health and genetic data of subjects. It should also be possible to further process such personal data by the same controller for **specific** scientific research purposes, **in compliance with Article 93**.

Article 58

Amendments to Regulation (EU) No 536/2014

Regulation (EU) 536/2014 is amended as follows:

- (1) Article 2 is amended as follows:

- (a) point (3) is replaced by the following:

‘(3) ‘Low-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions:

- (a) the investigational medicinal products, excluding placebos, are authorised;
- (b) according to the protocol of the clinical trial, the use of the investigational medicinal product is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products concerned; and
- (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;’

- (b) the following point (3a) is inserted:

‘(3a) ‘Minimal-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions:

- (a) the investigational medicinal products are authorised;

- (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of marketing authorisation; and
- (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned’;

(ba) the following point (3b) is inserted:

(3b) ‘multinational clinical trial’ means a clinical trial concerning more than one Member State;

- (c) points (12) and (13) are replaced by the following:

‘(12) ‘Member State concerned’ means the Member State where an application for authorisation of a clinical trial, ~~or~~ a combined study **or** of a substantial modification has been submitted under Chapters II, IIa or III of this Regulation respectively;’

‘(13) ‘Substantial modification’ means any change to any aspect of the clinical trial which is made after the notification of a decision referred to in Article 8 **or the conclusion of assessment of an application limited to aspects covered by Part I of the assessment report referred to in Article 11** in at least one Member State concerned and which is likely to have a substantial impact on the safety or rights of the subject or on the reliability and robustness of data generated in the clinical trial;’;

- (d) the following point (13a) is inserted:

‘(13a) ‘Parallel substantial modification’ means a substantial modification for which an application is submitted to a Member State concerned before a decision on a previous application for a substantial modification to the same clinical trial is notified by that Member State to the sponsor;’

- (e) points **(17) and** (21) ~~is~~**are** replaced by the following:

(17) ‘Subject’ means an individual, either a patient or a healthy volunteer, who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control;’

‘(21) ‘Informed consent’ means a subject’s free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject’s decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in a clinical trial, including consent given through the use of electronic systems, methods and processes, and signed electronically in accordance with Union law or equivalent standards;’

(f) the following points (36), to (47) are inserted:

(36) ‘Consideration’ means a justified concern or divergent view raised by a Member State concerned in the process of an assessment of an application for an authorisation of a clinical trial or for a substantial modification ~~on the aspects that,~~ if unresolved, will result in a negative decision on the clinical trial **application** or substantial modification application **from that Member State;**

(37) ‘Reporting Member State’ means the Member State concerned that:

(a) is responsible for the assessment and authorisation of the clinical trial application **and subsequent substantial modifications** in mono-national clinical trials **and mono-national combined studies.**

(b) is leading the assessment ~~for the authorisation~~ of a multinational clinical trial **application** ~~or of a~~ **and subsequent** substantial modifications regarding aspects covered by Part I of the **assessment report** ~~application dossier,~~ or

(c) is leading the assessment ~~for the authorisation~~ of a multinational combined study **application and subsequent substantial modifications regarding aspects covered by Part I of the assessment report;**

(38) ‘Investigational medicinal product core dossier’ means a dossier, containing ~~documents~~ **product-specific data and information** referred to in point (Ga), Part II of Annex I concerning the investigational medicinal product, established at the request of the sponsor in view of supporting the ~~development~~ **use** of the investigational medicinal product **in multiple clinical trials.**

- (39) ‘Core dossier depositary Member State’ means a Member State responsible for assessing suitability and completeness of the investigational medicinal product core dossier to be established and for the regulatory oversight of an already established dossier;
- (40) ‘Core dossier competent Member States’ means the Member States concerned for all corresponding clinical trials and the Member States indicated by a sponsor at the time of the initial request for the establishment of the investigational medicinal product core dossier;
- (41) ‘Corresponding clinical trial’ means a clinical trial **involving an** ~~tested to the~~ investigational medicinal product for which **the** ~~an~~ establishment of an investigational medicinal product core dossier has been requested and any subsequent clinical trial **involving** ~~tested to that~~ investigational medicinal product;
- (42) ‘Distribution’ means all activities, consisting of procuring, holding, supplying, shipping across Member States or exporting investigational medicinal product or auxiliary medicinal products, ~~including delivery of investigational and auxiliary medicinal products to the clinical trial participants;~~ **excluding the supply of such medicinal products to clinical trial subjects by persons authorised in accordance with the national law of the Member State concerned to supply medicinal products to the public.**
- (43) ‘~~Direct~~ **Delivery at a distance to the subject**’ means **the** controlled and documented ~~direct~~ delivery of ~~an~~ investigational medicinal products or auxiliary medicinal products to the subject’s place of residence **through persons authorised under the national law of the Member State to supply such medicinal products to the public or to the place of residence of the subject in** ~~a Member State, where the clinical trial has been authorised;~~

- (44) ‘Combined study’ means a clinical trial concerning one or more medicinal products combined with a performance study of one or more in vitro diagnostic medical devices, as defined in Article 2 point (42) of Regulation (EU) 2017/746 of the European Parliament and of the Council *and/or with a clinical investigation of one or more medical devices as defined in Article 2 point (45) of Regulation (EU) 2017/745 of the European Parliament and of the Council **;
- (45) ‘Regulatory sandbox’ means a regulatory framework that allows for the development and testing of innovative or targeted adapted regulatory approaches in a controlled environment pursuant to a specific plan, for a limited time and under regulatory supervision, that enables ~~innovation-driven~~ innovative approaches to ~~an~~ the authorisation and conduct of clinical trials including combined studies that otherwise would not be possible ~~or appropriate~~ given the current legal framework;’
- (46) ‘AI system’ means AI system as defined in Article 3(1) of Regulation (EU) 2024/1689 of the European Parliament and of the Council***;
- (47) ‘serious cross-border threat to health’ means serious cross-border threat to health as defined in Article 3(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council****‘

* Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (JO 5.5.2017, L117/176., ELI: <http://data.europa.eu/eli/reg/2017/746/oj>).

** 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 (JO 5.5.2017, L 117/1., ELI: <http://data.europa.eu/eli/reg/2017/745/oj>).

- *** Regulation (EU) 2024/1689 of the European Parliament and of the Council of 13 June 2024 laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828 (OJ L, 2024/1689, 12.7.2024, ELI: <http://data.europa.eu/eli/reg/2024/1689/oj>)
- **** Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26, <http://data.europa.eu/eli/reg/2022/2371/oj>).

(2) Article 3 is replaced by the following:

‘Article 3.

General principles

1. A clinical trial may be conducted only if:
 - (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and
 - (b) it is designed to generate reliable and robust data.
2. Member States concerned shall cooperate closely and efficiently to ensure the effective and timely application of the provisions of this Regulation. **In multinational clinical trials, all the Member States concerned including the reporting Member State shall cooperate in good faith and in a spirit of mutual trust and reliance.**
3. ~~Member States shall take into account whether a clinical trial is a minimal intervention or low intervention clinical trial and, where this is the case, adapt the regulatory requirements throughout the lifecycle of such clinical trial, in particular with regard to the application dossier, the authorisation procedures, the safety reporting and oversight.~~ **Minimal-intervention or low-intervention clinical trials shall be subject to adapted regulatory requirements throughout the lifecycle of such clinical trials as provided for in this Regulation.**

- (3) Articles 4 and 5 are replaced by the following:

'Article 4.

Prior authorisation

A clinical trial shall be conducted only if it has been authorised by the Member State concerned in accordance with this Regulation. Applications for an authorisation shall be subject to scientific and ethical review.

~~In clinical trials concerning more than one Member States (multinational clinical trials), all the Member States concerned including the reporting Member State shall cooperate in good faith and in spirit of mutual trust and reliance. The reporting Member State shall have a leading role in the assessments~~ **of multinational clinical trials.**

The reporting Member State shall involve its ethics committee in the assessment of ethical aspects of Part I of the application dossier referred to in Article 6. The ethical review **of Part II of the application dossier referred to in Article 7** shall be performed by an ethics committee **in each Member State concerned** in accordance with the law of **their** Member State. ~~The reporting Member State shall involve its ethics committee in the assessment of ethical aspects of Part I of the application dossier referred to in Article 6~~

Each Member State shall ensure that the organisation, timelines and procedures for the review **of the application** ~~by ethics committees~~ are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial and substantial modifications thereof.

Article 5

Submission of an application

1. In order to obtain an authorisation, the sponsor shall submit an application dossier **referred to in Article 25** to the intended Member States concerned throughout the Portal referred to in Article 80 ('the EU portal'). ~~referred to in Article 25.~~ The date on which the sponsor submits the application for an authorisation of a clinical trial is referred to within this Chapter as the submission date.

2. The authorisation procedure of a clinical trial consists of three steps:
- (a) a validation of the application dossier, as set out in Article 5b;
 - (b) an assessment, that consists of:
 - an assessment of Part I, as set out in Article 6, of the elements of the application dossier listed in Part I of Annex I, that constitute Part I of the assessment report dossier, and
 - an assessment of Part II, as set out Article 7 of the application dossier, of the elements of the application dossier, listed in Part II of Annex I, that constitute Part II of the application dossier assessment report.
 - (c) a decision resulting in either an authorisation, conditional authorisation or refusal of an authorisation, as set out in Article 8.’

(4) the following Articles 5a and Article 5b are inserted:

“Article 5a.

Appointment of the reporting Member State

1. In clinical trials concerning only one Member State, this Member State is the reporting Member State.
2. In clinical trials concerning more than one Member States, the sponsor shall propose one of the Member States concerned as the reporting Member State. All Member States concerned willing to become the reporting Member State shall declare their willingness through the EU portal.

The sponsor shall, when applying for a low-intervention clinical trial propose one of the Member States concerned where the use of the investigational medicinal product is evidence-based as a reporting Member State.

3. If the proposed Member State accepts the proposal by expressing willingness to become the reporting Member State, it shall be the reporting Member State.
4. If the proposed Member State does not accept the proposal, the following rules shall apply, and their application shall be supported by the EU Portal:

- (a) where there is only one other Member State concerned willing to become the reporting Member State, that Member State shall become the reporting Member State;
 - (b) where there is more than one Member State concerned willing to become the reporting Member State or none of the Member States concerned is willing to become the reporting Member State, the reporting Member State shall be designated automatically by the EU Portal in application of the recommendation referred to in article **85(5)(c)**. 85(2)(e)-
5. Within three days from the submission date, all Member States concerned, the sponsor and the reporting Member State shall be notified by the EU Portal of the appointment of the reporting Member State.

Article 5b -

Validation of Part I of the application dossier

1. Within seven days from the submission date, the reporting Member State shall validate Part I of application dossier referred to in Article 6 and notify the sponsor, through the EU portal, of the following:
- (a) whether the clinical trial applied for falls within the scope of this Regulation;
 - (b) whether the application dossier is complete in accordance with Part I of Annex I;
 - (c) whether ~~it confirms that~~ the clinical trial is **suitable for assessment as** a minimal-intervention or a low-intervention clinical trial, respectively, if such a claim was made by the sponsor.

Notwithstanding paragraph 2a of Article 6, the competent authority and ethics committee of the reporting Member State shall be involved in the validation of Part I of all application dossiers, including where the sponsor has claimed that the clinical trial is a minimal-intervention clinical trial.

2. Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 1, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete and, if applicable, the clinical trial shall be considered **suitable for assessment as** a minimal-intervention or low-intervention clinical trial.
3. Where the reporting Member State finds that the application dossier is not complete, or that the clinical trial applied for does not fall within the scope of this Regulation, or, if applicable, has doubts whether the clinical trial is a minimal-intervention or low-intervention clinical trial, the reporting Member State shall:
 - (a) inform the sponsor thereof through the EU portal and shall set a deadline of maximum seven days for the sponsor to comment on the application or to complete the application dossier through the EU portal;
 - (b) within **21 days from the submission date** ~~seven days from the submission of the comments or the completed application dossier referred to in point (a)~~ notify the sponsor as to whether or not the application complies with the requirements set out in paragraph 1 points (a), (b) and (c).

In case the reporting Member State requests the sponsor to comment on the application pursuant to this paragraph, the period referred to in paragraph 1 may be extended by a ~~maximum of 14~~ **up to 21** days **from the submission date**.

4. Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 3, point (b), the clinical trial applied for shall be deemed to fall within the scope of this Regulation, the application dossier shall be considered complete in accordance with Part I of Annex I and the clinical trials ~~is~~ **shall be** deemed to be **suitable for assessment as** a minimal-intervention or a low-intervention clinical trial, if claimed by the sponsor.

5. Where the sponsor has not provided comments or completed the application dossier within the period referred to in paragraph 3, point (a), **or where the reporting Member State concludes that insufficient justification has been provided to support a sponsor's claim that a clinical trial is a minimal-intervention or a low-intervention clinical trial,** the application shall be deemed to have lapsed in all Member States concerned.
6. For the purpose of this Chapter, the date on which the sponsor is notified in accordance with paragraph 1 or paragraph 3, point (b) shall be the validation date of the application. Where the sponsor is not notified within these time periods, the validation date shall be the last day of respective periods referred to in paragraph 1 or paragraph 3, point (b)."

(5) Article 6 is replaced by the following:

'Article 6

Assessment report – Aspects covered by Part I of the assessment report

1. The reporting Member State shall assess the application relying on the information and the documents listed in Part I of Annex I, with regard to the following aspects:
- (a) compliance with Chapter V as with respect to the following:
 - (i) the anticipated therapeutic and public health benefits taking account of all of the following:
 - characteristic of and knowledge about the investigational medicinal products;

- relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point 17(y) of Part I of Annex I; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; where applicable, taking into account any **decision adopted** ~~opinion formulated by the Paediatric Committee~~ **Agency** on ~~a~~ paediatric investigational plan in accordance with Chapter VII of Regulation (EU) .../...[*reference to be added after adoption cf. COM(2023)196final*];
- **whether the clinical trial is a minimal-intervention or a low-intervention clinical trial, respectively, if such a claim was made by the sponsor**
- reliability and robustness of the data generated in clinical trial, taking into account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;
- (ii) risk and inconveniencies for the subjects, taking into account all of the following:
 - characteristic of and knowledge about the investigational medicinal product and the auxiliary medicinal product;
 - **the** characteristics of the **intervention** ~~investigational medicinal product~~ **compared to normal clinical practice;**
 - safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;
 - risk to subjects' health posed by the medical condition for which the investigational medicinal product is being investigated;
 - aspects related to the protection of the subjects' safety, well-being and fundamental rights as a clinical trial participant.

- (b) compliance with the requirements concerning the manufacturing and import of investigational medicinal products **and auxiliary medicinal products** set out in Chapter IX;
- (c) compliance with the labelling requirements set out in Chapter X;
- (d) completeness and adequacy of the investigator's brochure.

~~The adequacy of the translations of the documents, when translations are required pursuant to Article 26 and Article 69, submitted in Part I shall be assessed in Part II.~~

2. The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.

The ethics committee of the reporting Member State shall review, from the ethical perspective, aspects covered by Part I of the assessment report. That ethical review shall complement the scientific and regulatory assessment and shall cover Part I of the application dossier in order to evaluate whether the subjects' rights, safety and well-being are being ensured in the clinical trial.²²

- 2a. Notwithstanding **article 5b and** paragraph 2 **of this article**, where the clinical trial is a minimal-intervention clinical trial, the assessment of the reporting Member State shall be limited to an ethical review by its ethics committee of the aspects referred to **in** points (a), **(c)** and **(d)** of paragraph 1.
3. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:
 - (a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation;
 - (b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or
 - (c) the conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation.

4. The reporting Member state shall submit, through EU portal, the final Part I of the assessment report, including its conclusions, to the sponsors and to the other Member States concerned within 42 days from the submission date.
5. For clinical trials involving more than one Member State concerned, the assessment process shall include three phases:
 - (a) an initial assessment phase within 28 days from the submission date;
 - (b) a review phase within ~~seven days from the end of the initial assessment~~ **35 days from the submission date;**
 - (c) a consolidation phase within ~~seven days from the end date of the review phase~~ **42 days from the submission date.**

During the initial assessment phase, the reporting Member State shall assess Part I of the application dossier and draw up a draft Part I of the assessment report and circulate it to all other Member States concerned within 28 days from the submission date.

During the review phase, ~~within seven days from the circulation of the draft assessment report~~ **within 35 days from the submission date** all Member States concerned shall review the application based on the draft Part I of the assessment report and shall share considerations ~~for their Member States~~ relevant to the application. ~~The e~~**C**onsiderations may be raised only on one of the following grounds:

- (a) one of the grounds referred to in Article 8(2);
- (b) issues that would lead to a negative opinion of the ethics committee of the Member State concerned.

When raising a consideration, Member States concerned shall justify why the consideration has been raised in line with the above grounds.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned and finalise Part I of the assessment report and shall record how all considerations have been dealt with. The reporting Member State shall submit the final Part I of the assessment report to the sponsor and all other Member States concerned within ~~seven days from the end of the review phase.~~ **42 days from the submission date.**

- 5a. Where the clinical trial is a minimal-intervention clinical trial, other Member States concerned may only raise during the review phase considerations referred to in paragraph 5 related to ethical aspects of the draft assessment report.”
6. For the purpose of this Chapter, the date on which the final Part I of the assessment report is submitted by the reporting Member State to the sponsor and to the other Member States concerned through the EU portal shall be the reporting date.”
7. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor, the reporting Member State may extend the period referred to in paragraph 4 by ~~maximum of~~ **up to 70 days from the submission date.**

The sponsor shall submit the requested information within the period set by the reporting Member State which shall not exceed 14 days from the receipt of the request. **156 days from the submission date]**

Upon receipt of the requested additional information, the Member State concerned shall review **the** additional information provided by the sponsor and shall identify and share with the reporting Member State any unaddressed considerations, relevant for the application. The coordinated review shall be performed within ~~maximum 7 days of~~ **from** the receipt of the additional information **[63 days from the submission date]** and the further consolidation shall be performed within ~~maximum seven 14~~ days **from the receipt of the additional information [70 days from the submission date]**. ~~of the end of the coordinated review.~~ When finalising Part I of the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how the considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and additional information shall be submitted through the EU Portal.’

(6) Article 7 is replaced by the following:

‘Article 7

Assessment report – Aspects covered by Part II of the application dossier

1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects. Such assessment shall constitute Part II of the assessment report:
 - (a) compliance with the requirements for informed consent set out in Chapter V;
 - (b) compliance of the arrangements for rewarding or compensating subjects with the requirements set out in Chapter V, **and investigators**;
 - (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;
 - (d) compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council*;

- (e) compliance with Article 49;
 - (f) compliance with Article 50;
 - (g) compliance with Article 76;
 - (h) compliance with applicable rules for the collection, storage and future use of biological samples of the subject;
 - (i) ~~accuracy of the translations of the documents and information submitted in Part I of the application dossier, when such documents are required to be submitted in the national language in accordance with Article 26 and 69.~~
2. Each Member State concerned shall complete the assessment within 42 days from the submission date and submit, through the EU portal, Part II of the assessment report, including its conclusions, to the sponsor. **Where the due date for Part II would fall earlier than that for Part I, the assessment shall be completed by the due date applicable to Part I.**

Where a Member State concerned finds that the application dossier is not complete it shall request the sponsor to comment on the application or to complete the application dossier as part of the part II assessment through the EU portal.

Each Member State concerned may within the period referred to in this paragraph, and through EU portal, request on duly justified grounds additional information, from the sponsor regarding the aspects covered in paragraph 1 or to request to complement the documentation, required pursuant to Part II of Annex I, if such documentation is missing or documentation provided is not adequate or is incomplete.

The Member State concerned may decide within 28 days of the submission date to rely on the ethical review of the ethics committee of the reporting Member State of the common elements of the application dossier of Part II and inform the sponsor accordingly **within 28 days from the submission date.**

3. Each Member State concerned may extend the assessment period referred to in paragraph 2 ~~by a maximum of 28~~ **up to 70 days from the submission date:**
- (a) to requests additional documentation or information, as referred in paragraph 2, from the sponsor regarding Part II of the assessment for its territory;
 - (b) to align with the timeline for the assessment referred to in Article 6, when it has been extended to allow for a request for information by the reporting Member State related to Part I assessment and its review.

The request for additional information and additional information shall be submitted through the EU Portal. Member State concerned shall not request documentation or information, which is submitted and assessed under Part I.

The sponsor shall submit the requested additional information and documentation within the period set by the Member State concerned which shall not exceed 14 days from the receipt of the request **[56 days from the submission date]**.

Upon receipt of the additional information and documentation, the Member State concerned shall complete its assessment within maximum of 14 days from the submission of the requested information by the sponsor **[70 days from the submission date]**.

Where the sponsor does not provide additional information and documentation within the period set by the Member State concerned in accordance with this paragraph, the application shall be deemed to have lapsed in that Member State concerned.

* Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ_L 119, 4.5.2016.,
ELI: <http://data.europa.eu/eli/reg/2016/679/oj>.’

(7) in Article 8, paragraphs 1 and 2 are replaced by the following:

1. Each Member State concerned shall notify the sponsor through the EU portal and by way of one single decision as to whether the clinical trial is authorised, authorised subject to conditions, or whether authorisation is refused.

The notification shall be made within five days from the reporting date or from the last day of the assessment referred to in Article 7, whichever is later.

2. Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member States concerned.

A clinical trial subject to conditions may start, unless the Member State concerned specified **as part of a condition** that the condition is suspensive. ~~Unless otherwise specified, a fulfilment of the condition shall not require a submission of a request for~~ **authorisation of** a substantial modification **is required before the clinical trial commences.**

Notwithstanding the first subparagraph of this paragraph, a Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds, provided that the corresponding consideration was raised during the process pursuant to Article 6(5), **third subparagraph, point (b)** and the Member State concerned considers that it was not sufficiently addressed:

- (a) participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned; or
- (b) infringement of its national law as referred to in Article 90.

Where a Member State concerned disagrees with the conclusion, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.’

- (8) Article 9 is replaced by the following:

‘Article 9

Persons assessing the application

1. Member States shall ensure, including through the institutional safeguards, that persons validating and assessing the application do not have conflicts of interest, are independent of the sponsors, or the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence and ensure their sufficient independence in performance of their tasks.

In order to guarantee independency and transparency, the Member States shall ensure that persons validating and assessing the application as regards the aspects covered in Parts I and II of the assessment report have no financial or personal interests which could affect their impartiality. These persons shall make an annual declaration of their financial interest.

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

These persons shall be sufficiently equipped and empowered to perform their tasks.

3. At least one layperson shall participate in the assessment.’

(9) in Article 10, the following paragraph 6 is added:

6. Where potential subjects of a clinical trial belong to vulnerable populations, Member States concerned and sponsors shall consider and weigh the harms and benefits of their ~~inclusion as opposed to their exclusion from~~ **participation in** a clinical trial. **Without prejudice to articles 31 and 32 of this Regulation, the sponsors shall evaluate whether the exclusion of those subjects from a clinical trial could inadvertently perpetuate or exacerbate their vulnerabilities, particularly in relation to their specific health needs and shall include the justification of the inclusion or exclusion of the vulnerable population in the protocol. Member States concerned shall verify the sponsor's evaluation.**

~~The Member States concerned and sponsors shall assess in particular whether the exclusion of those subjects from a clinical trial could inadvertently perpetuate or exacerbate their vulnerabilities, particularly in relation to their specific health needs.~~

(10) Article 11 is replaced by the following:

‘Article 11

Submission and assessment of applications limited to aspects covered by Part I of the assessment report

1. Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the conclusion shall be limited to the aspects covered by Part I of the assessment report.

After the notification of the conclusion on the aspects covered by Part I of the assessment report, the sponsor may, within two years, apply for an authorisation limited to aspects covered by Part II of the assessment report.

Where the sponsor submits only Part I of the application dossier to all of the Member States concerned, the sponsor shall declare at the time of the first submission of Part II of the application dossier to any of the Member States concerned that the sponsor is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report. If an update of Part I of the application dossier is necessary, the sponsor shall submit a substantial modification of Part I of the application dossier, at the latest, at the same time as the submission of Part II of the application dossier to at least one of the Member States concerned.

The Part II of the application dossier shall be assessed in accordance with Article 7 and the Member State concerned shall notify the decision on clinical trial in accordance with Article 8.

In those Member States concerned where the sponsor does not apply for an authorisation limited to aspects covered by Part II of the assessment report within two years, the application on the aspects covered by Part I of the assessment report shall be deemed to have lapsed.

2. When the sponsor submits a substantial modification of Part I of the application dossier with regard to a clinical trial that is subject to a request referred to in paragraph 1 ~~and has been authorised or authorised subject to conditions by at least one Member State concerned~~, all Member States concerned ~~that received~~ where the conclusion on the initial application is still applicable, including those who have not yet received Part II of the application, shall participate in the assessment of that substantial modification in accordance with Article 18 or 22 as appropriate.’

(11) Article 14 is amended as follows:

(a) paragraph 1 is replaced by the following:

‘1. Where the sponsor wishes to extend an authorised clinical trial to another Member State(s) (additional Member State(s) concerned), the sponsor shall submit an application dossier to ~~that~~ **those** Member State(s) through the EU portal.

The application dossier may be submitted only after the notification date of the ~~first~~ initial authorisation decision by at least one Member State concerned.

(b) paragraph 3 is replaced by the following:

‘3. The additional Member State(s) concerned shall notify the sponsor, through the EU portal, within 47 days from the date of submission of the application dossier referred to in paragraph 1 of this Article, by way of one single decision **in each additional Member State concerned** as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused. Article 8(2), (3), (4) and (5) apply to the decisionss of the additional Member State(s) concerned.’

(c) paragraph 4 is deleted;

(d) paragraphs 5 to 8 are replaced by the following:

‘5. Within ~~35~~**42** days following the submission date referred to in paragraph 1, the additional Member State(s) concerned may communicate to the reporting Member State and the other Member States concerned any considerations through the EU ~~P~~**p**ortal.’

(e) — paragraphs 6, 7 and 8 are replaced by the following:

- ‘6. **Within 42 days from the submission date**, between the submission date referred to in paragraph 1 and the expiry of the period referred to in paragraph 3, only the reporting Member State may request additional information from the sponsor concerning the aspects covered in Part I of the assessment report, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraphs, the reporting Member State may extend the period ~~referred to in the first subparagraph of paragraph 3~~ by a maximum of ~~70~~**28** days **from the submission date**.

The sponsor shall submit the requested additional information within the period set by the reporting Member State, which shall not exceed ~~14~~ **56** days from **the submission date** ~~receipt of the request~~.

Upon receipt of the additional information the reporting Member State, the additional Member State(s) concerned and all other Member States concerned shall review any additional information provided by the sponsor together with the original application and shall share any unaddressed considerations relevant to the application. The coordinated review shall be performed within a maximum of ~~seven~~ **7** days from the receipt of the additional information **[63 days from the submission date]** and the further consolidation shall be performed within a maximum of **14 days from the receipt of the additional information [70 days from the submission date]**. ~~seven days from the end of the coordinated review~~. The reporting Member State shall take due account of the considerations of the Member States concerned and shall record how the considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

7. The additional Member State(s) concerned shall assess, for its own territory, the aspects covered in Part II of the assessment report and submit Part II assessment report, including its conclusions, through the EU portal, to the sponsor.

Within **42 days from the submission date** ~~the period referred to in paragraph 3, the~~ additional Member State(s) may request, through the EU portal, with justified reasons, additional information from the sponsor regarding aspects covered in Part II of the assessment report as far as its their own territories ~~y~~ is are concerned.’

8. For the purpose of obtaining and reviewing the additional information referred to in paragraph 7 the additional Member State(s) concerned may extend the period referred to in paragraph 5 by a maximum of ~~28~~ **70** days **from the submission date**.

The sponsor shall submit the requested additional information within the period set ~~be~~ by the additional Member State(s) concerned, which shall not exceed 14 days from the receipt of the request **56 days from the submission date**.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within ~~a maximum of 14~~ **70** days **of the submission date**.

Where the sponsor does not provide additional information within the period set by ~~the~~ an additional Member State concerned in accordance with second subparagraph, the application shall be deemed to have lapsed in ~~the~~ that additional Member State concerned.’

~~(e)(f)~~ paragraphs 9 and 10 are deleted;

~~(f)~~ (g) paragraphs 11 and 12 are replaced by the following:

- ‘11. Where ~~the~~ an additional Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 3, or in case that period has been extended in accordance with paragraph 6 or 8 and where that additional Member State concerned has not notified the sponsor of its decision within the extended period, the conclusion on Part I of the assessment report shall be deemed to be the decision of that additional Member State concerned on the application for authorisation of the clinical trial.’
12. A sponsor shall not submit an application dossier in accordance with this Article where a procedure for a substantial modification of Part I of the assessment report, set out in Chapter III, is pending as regards that clinical trial.’

(12) the following Article 14a is inserted:

'Article 14a

Appointment of a new reporting Member State

1. The reporting Member State may initiate the procedure for an appointment of a new reporting Member State if:
 - (a) the reporting Member State has notified its decision refusing the authorisation of the clinical trial **based on a negative opinion on the assessment of Part II of the application dossier in the reporting Member State but where there was a positive opinion on the assessment of Part I of the application dossier;** or
 - (b) the clinical trial is no longer taking place in the reporting Member State **including when the sponsor has submitted an end of trial notification in line with Article 37 notifying the end of the trial in the reporting Member State for reasons not affecting the benefit-risk balance, and the trial is ongoing in at least one other Member State concerned**
2. The procedure can only be launched after the clinical trial has been authorised in at least one Member State concerned.
3. The reporting Member State shall notify the sponsor and other Member States concerned of its intention to cease to be a reporting Member State.
4. The Member States concerned shall declare their willingness to become new reporting Member State. The selection of new reporting Member State shall follow the rules established Article 5a (4) and (5).

5. Following the initiation of the procedure for the appointment of a new reporting Member State, the initial reporting Member State shall continue to carry out its tasks until all of the ongoing assessments and records are completed and the respective final assessment reports are submitted to the EU portal.
6. The new reporting Member State shall become responsible for the assessment of any application related to Part I of the assessment report, including an application based on Article 14, that has been submitted after it has been notified as the reporting Member State to the sponsor and all Member States concerned by the EU portal.’

(13) the following Chapter IIa is inserted:

‘Chapter IIa

SPECIAL AUTHORISATION PROCEDURES

Article 14b

*Accelerated procedure for the authorisation of multinational clinical trials ~~in the context of~~
public health emergencies*

- 1. By way of derogation from Articles 5b, 6, 7 and 8 of this Regulation, accelerated authorisation procedures for multinational clinical trials falling in one of the following categories shall be subject to the requirements laid down in this Article:**
- (a) **multinational clinical trials related to a recognised public health emergency at Union level in accordance with Article 23(1) of Regulation (EU) 2022/2371; or**
 - (b) **multinational clinical trials aimed at addressing the emergence or development of a serious cross-border threat to health as defined in Article 3(1) of Regulation 2022/2371 that is likely to lead to the recognition of a public health emergency at Union level in accordance with Article 23(1) of that Regulation;**

- 2. By way of derogation from Articles 5b, 6, 7 and 8 of this Regulation, accelerated authorisation procedures for multinational clinical trials falling in one of the following categories may be subject to the requirements laid down in this Article:**
- (a) multinational clinical trials related to biodefence or addressing a need related to the protection of national security and defence; or**
 - (b) multinational clinical trials involving investigational medicinal products in the initial stages of testing (phase I or phase I-II).**

The timelines for the accelerated procedure referred to in paragraph 1, points (a) to (c) shall be based on, and in any case, not exceed, the timelines referred to in articles 17, 18 and 19 of this Regulation. Such timelines shall be detailed in the delegated acts referred to in paragraph 5.

- 3. The accelerated procedure for the authorisation of multinational clinical trials referred to in paragraph 1(a) is as follows:**

1-(a) During a recognised public health emergency at Union level pursuant to Article 23 of Regulation (EU) 2022/2371 of the European Parliament and of the Council, Member States shall apply ~~an~~ **the** accelerated procedure for the authorisation of multinational clinical trials for medicinal products intended for the treatment, prevention or medical diagnosis of the disease or condition which are directly related to the public health emergency.

2. ~~(b)~~ To address an emergence or development of a serious cross-border threat to health as defined in Article 3(1) of Regulation 2022/2371 that is likely to lead to the recognition of a public health emergency at Union level in accordance with Article 23(1) of Regulation (EU) 2022/2371, Member States shall apply ~~an~~ the accelerated procedure for the authorisation of multinational clinical trials when this procedure is declared applicable in accordance with the criteria referred to in point (c) of this ~~in paragraph 3 of this Article~~. The application of the accelerated procedure shall aim to ensure the availability of medicinal products in order to prevent or swiftly contain the emerging serious cross-border health threat, to provide timely treatment options grounded in scientifically robust evidence or to facilitate medical diagnosis of the disease or condition directly related to the specific serious cross-border health threat.

3. (c) The Commission shall, by means of implementing acts, lay down the detailed criteria and the processes for declaring the applicability of the accelerated authorisation procedure to address an emergence or development of serious cross-border threat to health that is likely to lead to the recognition of a public health emergency at Union level in accordance with Article 23 (1) of Regulation (EU) 2022/2371.

The criteria for declaring the applicability of an accelerated authorisation procedure shall at least include the epidemiological situation and its dynamics as well as the availability of treatment, prevention and diagnostics options addressing the emerging serious cross-border threat to health. The process of declaring applicability of the accelerated authorisation procedure shall involve consultations with relevant Union agencies, expert groups and advisory bodies in the field of public health and clinical trials.

The implementing acts referred to in the first subparagraph shall be adopted in accordance with the examination procedure referred to in Article 88.

4. (d) When submitting the application for the clinical trial authorisation during a public health emergency as referred to in paragraph **3(a)** or when the accelerated procedure referred to in paragraph **3(b)** is declared applicable to address an emerging serious cross-border health threat, pursuant to the procedure referred to in paragraph **3(c)**, the sponsor shall indicate whether the investigational medicinal products are intended for the treatment, prevention or medical diagnosis of a disease or a condition directly related to the specific serious cross-border threat to health. The reporting Member State shall confirm whether the accelerated procedure is applicable to the clinical trial application.

4. The accelerated procedure for the authorisation of multinational clinical trials referred to in paragraph 1(b) and 1(c) is as follows:

(a) Member States may apply an accelerated authorisation procedure for multinational clinical trial applications involving investigational medicinal products in the initial stages of clinical development (phase I and phase I-II clinical trials).

(b) Member States may apply an accelerated authorisation procedure for multinational clinical trial applications concerning clinical trials related to biodefence or addressing a need related to the protection of national security and defence.

(c) The Clinical Trials Coordination and Advisory Group (CTAG) referred to in Article 85 shall publish a list of Member States that expressed their interest to take the role of reporting Member States or to participate as other Member States concerned in the voluntary accelerated authorisation procedure referred to in points (a) and (b) of this paragraph.

d. When submitting an application dossier, the sponsor shall indicate whether the accelerated procedure, referred to in points (a) and (b) of this paragraph is requested, and shall propose a reporting Member State from the list of willing Member States referred to in point c of this paragraph. The reporting Member State shall confirm whether the accelerated procedure is applicable or not, taking in to account the qualification criteria laid out in the delegated act referred to in paragraph 5 of this article. Where no request is made, or where the request is rejected, the standard timelines provided for in this Regulation shall apply.

5. The Commission shall adopt delegated acts in accordance with Article 89 to supplement this Regulation by setting out:

- ~~(a)~~ the procedures for ~~an~~ **the** accelerated authorisation of multinational clinical trials **referred to in paragraph 1 points (a), (b) and (c),** including **the integrated ethical review,** timelines, **and the** criteria for evaluating whether a clinical trial qualifies for ~~an~~ **the** accelerated procedure.
- ~~(b)~~ **simplified requirements for the application dossier and regulatory flexibilities in relation to clinical trials referred to in paragraph 1, point (a).**
~~and an integrated ethical review, and by laying down simplified requirements for the application dossier.~~

This may include allowing sponsors to apply the following regulatory flexibilities:

- (i) **flexibility in the timing of data submission for assessment**
- (ii) **flexibility in protocol design to avoid protocol breaches and deviations**
- (iii) **the possibility to adapt clinical trial endpoints and re-estimate sample size as new data becomes available**
- (iv) **adaptations to safety data collection**
- (v) **remote procedures in accordance with Article 29 and direct delivery to the subjects in accordance with Article 50a**

Such simplified application dossier requirements and regulatory flexibilities shall not compromise subject safety or data robustness and reliability.

Article 14c

Combined studies

1. This Article applies to combined studies in which a clinical trial is combined with a performance study of an *in vitro* diagnostic medical device **that would otherwise be** subject to **separate** authorisation pursuant to Article 58(1) of Regulation (EU) 2017/746, **and** or is combined with a clinical investigation of a medical device that **would otherwise be** is subject to **separate** authorisation **pursuant** according to Article 62 of Regulation (EU) 2017/745.
2. ~~By way of derogation from Article 5, the~~ The sponsor of a combined study referred to in paragraph 1, which is to be conducted in one or more Member States, may submit a single application for authorisation **of the combined study under this regulation.**

Regulations (EU) 2017/746 and Regulation (EU) 2017/745 shall not apply where a single application has been submitted. Unless specified otherwise, provisions related to clinical trials in this Regulation shall also apply to a clinical trial that is part of a combined study.

3. The single application referred to in paragraph 2 shall be submitted electronically through the EU Portal to all Member States in which the combined study is to be conducted ('Member States concerned'). Where a combined study has more than one sponsor, the sponsors shall designate one coordinating sponsor. **The coordinating sponsor shall be the contact point for all questions from subjects, investigators or any Member State(s) concerned regarding the combined study and shall be responsible for providing answers to them following consultation, as appropriate, with the other sponsor(s). The designation of the coordinating sponsor shall be supported by a written contract between the coordinating sponsor and the other sponsor(s) clearly specifying the roles and responsibilities of each sponsor.**

4. The Member States concerned shall assess the single application by means of a coordinated assessment procedure under the direction of a reporting Member State chosen from among the Member States concerned. If a combined study involves only one Member State, that Member State shall be the reporting Member State.
5. The coordinated assessment procedure shall **be based on the assessment procedure provided for in Chapters II and III of this Regulation and shall** include the assessment by the competent authorities **for clinical trials, clinical investigations and performance studies as appropriate** and review by ethics committees **in the Member States concerned**. During the assessment procedure, the Member States concerned may only raise considerations related to the following:
- (a) the grounds referred to in **paragraph 6 of this** Article 14a(5) ~~of this Regulation, Article 78(8) of Regulation (EU) 2017/746⁵ or Article 74(8) of Regulation (EU) 2017/745⁶~~; or
 - (b) issues that would lead to ethics committee of the Member State concerned issuing a negative opinion.

When raising a consideration, Member States concerned shall justify why the consideration has been raised in line with the above grounds.

6. Where the conclusion of the reporting Member State as regards the area of coordinated assessment is that the conduct of the combined study 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 of this paragraph, a Member State concerned may disagree with the conclusion of the reporting Member State concerning the area of coordinated assessment but only on one of the following grounds, provided that the corresponding consideration was raised during the assessment process and the Member State concerned has substantiated comments that were not sufficiently addressed:

- (a) participation in the combined study would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
- (b) infringement of its national law;
- (c) with regard to the assessment of the medical device or in vitro medical device, grounds referred to in ~~Article 78(8) of Regulation 2017/746~~ or **Article 78(8)** ~~74(8)~~ of Regulation (EU) 2017/745 **or Article 74(8) of Regulation (EU) 2017/746**, respectively

- 7 Where a Member State concerned disagrees with the conclusion on the basis of paragraph ~~6~~ **5**, it shall communicate its disagreement, together with a detailed justification, through the EU Portal, to the Commission, to all other Member States concerned, and to the coordinating sponsor referred to in paragraph ~~3~~ **2**.
8. Each Member State concerned shall issue a single decision as to whether the combined study is authorised, whether it is authorised subject to conditions, or whether authorisation is refused and shall notify the coordinating sponsor referred to in paragraph ~~2~~ **3**.

9. ~~The~~ Commission shall, by means of ~~a~~ delegated acts in accordance with Article 89, ~~amend or~~ supplement, as necessary, the provisions of Chapters II to V, VII, XIII, XIV and XVI and Articles 71 and 72 of this Regulation in order to:

- (a) enable a streamlined procedure for an authorisation of combined studies, including the coordinated assessment of initial applications, coordinated assessment of the request for substantial modifications and additions of Member State concerned **taking into account paragraphs 3 to 8 of this article;**
- (b) set the requirements applicable during the conduct of the combined studies, **to ensure a consistent level of subject protection and safety reporting as would be required if the clinical trial, clinical investigation or performance study was not part of a combined study;**
- ~~(a)~~ **(c)** clarify the responsibilities of the combined studies' sponsors and investigators **taking into account paragraph 3 of this article and considering relevant sponsor and investigator responsibilities for clinical trials, clinical investigations or performance studies;**
- ~~(b)~~ **(d)** ensure **effective supervision of the conduct of the combined study by the Member State(s) concerned. The system of supervision should provide for the involvement of and cooperation between relevant national competent authorities in the oversight of combined studies and in considering any corrective measures deemed necessary to ensure compliance with the requirements for such studies;**
- ~~(c)~~ **(e)** determine the functionalities of the EU portal and EU database necessary to **facilitate interoperability between relevant information systems and** support application of this Article.

When doing so, the Commission shall seek to ensure that the regulatory and scientific requirements for combined studies are consistent where relevant with the requirements of this Regulation with respect to clinical trials, Regulation (EU) 2017/745 with respect to clinical investigations and Regulation (EU) 2017/746 with respect to performance studies, while at the same time avoiding conflicting obligations, unnecessary duplication or administrative overlap.

- ~~10. When doing so, the Commission shall take into consideration, where relevant, provisions of Chapter VI and Annex XV of Regulation (EU) 2017/745 or Chapter VI and Annexes XIII and XIV of Regulation (EU) 2017/746 concerning the investigational device(s) or device(s) for performance study which are covered by the combined study, as applicable.~~

~~Article 14d~~

~~Persons assessing the applications~~

~~Article 9 applies to assessments made under this Chapter.’~~

- (14) Article 16 is replaced by the following:

‘Article 16.

Submission of application

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal. The date on which the sponsor submitted the application for an authorisation of a substantial modification is referred to within this Chapter as the submission date.’;

(15) the following Article 16a is inserted:

'Article 16a
Parallel substantial modification

1. The sponsor may submit to the reporting Member State, through the EU portal, an application for a parallel substantial modification regarding aspects covered by Part I of the assessment report, prior to the notification of a decision on an ongoing assessment of a substantial modification in accordance with Article 19(1) or Article 23(1).
2. The sponsor may submit to the same Member State concerned, through the EU portal, an application for a parallel substantial modification of an aspect covered by Part II of the assessment report prior to the notification of a decision on an ongoing assessment of a substantial modification in accordance with Article 20(5) or Article 23(1) by the same Member State concerned.
3. The **EU Portal shall only facilitate the submission of parallel substantial modifications** ~~reporting Member State or Member state concerned, as applicable, shall accept the application for a parallel substantial modification if they~~ parallel substantial ~~modification~~ concerns distinct and independent aspects of the application dossier and may be assessed concurrently by the same Member State concerned or reporting Member State.
4. ~~When scope of the application for the parallel substantial modification covers both Part I and Part II of the assessment report, the sponsor shall seek the agreement of both, the reporting Member State and the relevant Member States concerned. The relevant Member State concerned may oppose the agreement if the substantial modification concerns aspects of Part II covered by an ongoing assessment.²~~

(16) Article 17 is amended as follows:

(a) paragraphs 1 and 2 are replaced by the following:

- ‘1. The reporting Member State for the authorisation of the substantial modification shall be the reporting Member State for the initial authorisation procedure **or the new reporting Member State appointed in accordance with Article 14a.**
2. Within ~~four~~**five** days from the submission date, the reporting Member State shall validate the application and notify the sponsor through the EU portal as to whether:
 - (a) the substantial modification concerns an aspect covered by Part I of the assessment report;
 - (b) the application dossier is complete in accordance with Annex II; and
 - ~~(c) in case of parallel substantial modification to Part I, whether such a parallel substantial modification is acceptable taking into account the requirements of Article 16a.~~

~~When applicable, in the context of a substantial modification of Part I, the Member State concerned shall verify whether the translation or translations in the national language or languages in accordance with the requirements of Articles 26 and 69 has or have been submitted as a substantial modification of Part II. Article 21 applies to the assessment of the accuracy of translations.’~~

(b) paragraph 4 is replaced by the following:

- ‘4. Where the reporting Member State finds that the application does not concern an aspect covered by Part I of the assessment report or that the application dossier is not complete ~~or, where applicable, that the parallel substantial modification is not acceptable~~, it shall inform the sponsor thereof though the EU portal **within five days of the submission date** and shall set a maximum of ~~four~~**five** days for the sponsor to comment on the application ~~of~~ **or** to complete the application dossier though the EU portal.

The reporting Member State shall notify the sponsor within 14 days from the submission date, as to whether or not the application complies with the requirements set out in paragraph 2, points (a) **and** (b)), ~~and when applicable point (c).~~

Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report, the application dossier shall be deemed to be complete ~~and, when applicable, the parallel substantial modification shall be deemed to be acceptable taking into account the requirements of Article 16a.~~

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all the Member States concerned.’

(17) Article 18 is amended as follows:

(aa) paragraph 1 is replaced by the following:

1. The reporting Member State shall assess the application with regard to any aspect covered by Part I of the assessment report and draw up a draft assessment report. Where a clinical trial has been previously designated as a minimal-intervention or a low-intervention clinical trial, the assessment will consider whether the proposed substantial modification would change that previous designation and if so whether previously adapted regulatory requirements particularly in relation to safety reporting and oversight also need to be amended.

(a) paragraphs 3 and 4 are replaced by the following:

‘3. The reporting Member State shall submit, through the EU portal, the final assessment report including its conclusions, to the sponsor and to the other Member States concerned within 28 days from the submission date.

For the purpose of this Article and of Articles 19 and 23, the reporting date shall be the date on which the final assessment report is submitted to the sponsor and the other Member States concerned.

4. For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:
- (a) an assessment phase performed by the reporting Member State within 21 days from the submission date. The assessment phase shall end when the reporting Member State circulates the draft assessment report;
 - (b) a review phase performed within ~~three~~**25** days from the submission date ~~end of the assessment phase~~, involving all the Member States concerned, and;
 - (c) a coordination phase performed within ~~four~~**28** days from the submission date ~~end of the review phase~~.

During the assessment phase, the reporting Member State shall develop a draft assessment report and circulate it to all the Member States concerned.

During the review phase, all Member States concerned shall review the application on the basis of the draft assessment report and shall share considerations for their Member State that are relevant to the application.

Considerations may only be raised on:

- one or more grounds referred to in Article 19(2)(~~2~~)**(1)** of this Regulation.
- on matters that would lead the ethics committee issuing negative opinion.

When raising a consideration, Member States concerned shall justify why the consideration has been raised in line with the above grounds.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalizing the assessment report and shall record how the considerations have been addressed. The reporting Member State shall submit the final assessment report to the sponsor and all the other Member States concerned by the reporting date.'

- (b) paragraph 5 is deleted;
- (c) paragraph 6 is replaced by the following:

'6. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of **up to 42**~~44~~ days **from the submission date**.

The sponsor shall submit the requested additional information within the period set by the reporting Member State. This period shall not extend beyond seven days from the receipt of the request.

Upon receipt of the additional information, the Member States concerned shall review any additional information provided by the sponsor and shall share any unaddressed considerations relevant to the application. The review shall be performed within a maximum of three days from the receipt of the additional information **[38 days from the submission date]** and further consolidation shall be performed within a maximum of seven days from the receipt of additional information from the sponsor **[42 days from the submission date]**. When finalising the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how the considerations have been dealt with.’;

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and the additional information shall be submitted through the EU Portal.

(18) Article 19 is amended as follows:

(a) paragraphs 1, ~~and 2~~ **and** 6 are replaced by the following:

‘1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date.

Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusions shall be deemed to be the conclusions of the Member State concerned.

A substantial modification subject to condition(s) may be implemented unless the Member State concerned specified that the condition is suspensive. ~~Unless otherwise specified, the fulfilment of the condition does not require a submission of a request for~~ **authorisation of another substantial modification is required before the changes proposed as part of the substantial modification subject to condition(s) can be implemented.**

Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds, provided that the consideration was raised during the process pursuant to Article 18(4) and it considers that it was not sufficiently addressed:

- (a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
 - (b) infringement of its national law as referred to in article 90.
2. Where the Member State concerned disagrees with the conclusion on the basis of **any of the grounds listed in the first paragraph** ~~the second subparagraph~~, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States and to the sponsor.

A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the ~~second~~ **first** paragraph or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for the entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.’

6. Where a clinical trial was previously designated as a minimal-intervention or a low-intervention clinical trial, and the outcome of the assessment of the substantial modification changes that previous designation, the reporting Member State will inform the sponsor who shall update the EU portal to reflect the change in the designation.

(19) Article 20 is amended as follows:

(a) paragraphs 1 and 2 are replaced by the following:

‘1. Within ~~four~~ **five** days from the submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:

- (a) whether the substantial modification concerns an aspect covered by Part II of the assessment report;
- (b) whether the application dossier is complete in accordance with Annex II;
- ~~(c) in case of parallel modification to Part I, whether the submission is acceptable taking into account the requirements of Article 16a.~~

‘2. Where the Member State concerned has not notified the sponsor within the period referred to in paragraph 1, the substantial modification applied for shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete. ~~and, when applicable, the parallel substantial modification shall be deemed to be acceptable taking into account the requirements of Article 16a.~~’

(b) in paragraph 3, the two first subparagraphs are replaced by the following:

‘Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application dossier is not complete, ~~or, where applicable, that the parallel substantial modification is not acceptable,~~ it shall inform the sponsor thereof through the EU portal and shall set a maximum of five days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within 14 days from the submission date the ~~reporting~~ Member State **concerned** shall notify the sponsor as to whether or not the application complies with the requirements set out in paragraph 1 points (a) **and**(b).~~and if applicable, (e).~~’

(c) in paragraph 5, the second and third subparagraphs are replaced by the following:

‘Notification shall be done by way of a single decision within 28 days from the submission date.

A substantial modification subject to condition(s) may be implemented unless the Member State concerned specified that the ~~condition is suspensive. Unless otherwise specified, a fulfilment of the condition does not require a submission of a request for~~ **authorisation of** another substantial modification **is required before the changes proposed as part of the substantial modification subject to condition(s) can be implemented..**’

- (d) in paragraph 6, the second, third and fourth subparagraphs are replaced by the following:

‘For the purpose of obtaining and reviewing this additional information from the sponsor, the Member State concerned may extend the period referred to in the paragraph 5, second subparagraph, by a maximum of up to 42 days from the submission date.

The sponsor shall submit the requested additional information within the period set by the Member State concerned, which shall not exceed ~~seven~~35 days from the submission date. ~~the receipt of the request.~~

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a ~~maximum seven~~ 42 days from the submission date.’;

- (20) in Article 21, paragraph 1 is replaced by the following:

- ‘1. Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the **Part I** application for an authorisation of that substantial modification shall be validated in accordance with Articles 17 ~~and 20.~~’;

Where a Member State concerned finds that the Part II application dossier is not complete in accordance with Annex II it shall request the sponsor to comment on the application or to complete the application dossier as part of the part II assessment through the EU portal.

(21) Article 22 is amended as follows:

(a) paragraph 1 is replaced by the following:

‘1. Each Member State concerned shall assess, for its own territory, the aspects of the substantial modification which are covered by Part II of the assessment report and submit, through the EU portal, that report, including its conclusion, to the sponsor within 28 days from the submission date. If the reporting Member State requested additional information regarding aspects covered by Part I of the assessment report as per Article 21(2) in conjunction with Article 18(6), or when a Member State concerned requests additional information from the sponsor regarding Part II aspects of the application, Member States concerned may extend this period ~~by 14 days~~ **up to 42 days from the submission date.**’

(b) paragraph 2 is deleted;

(c) paragraph 3 is replaced by the following:

‘3. The sponsor shall submit the requested additional information within the period set by the Member State concerned, which shall not exceed ~~seven~~ **35** days from the **submission date**~~the receipt of the request~~.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of ~~seven~~ **42** days from the submission **date** ~~of the requested information by the sponsor~~.

Where the due date for Part II would fall earlier than that for Part I, the assessment shall be completed by the due date applicable to Part I.

Where the sponsor does not provide the requested additional information within the period set by the Member State concerned the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.’

(22) Article 23 is amended as follows:

(a) in paragraph 1, the third subparagraph is replaced by the following:

‘A substantial modification subject to condition may be implemented unless the Member State concerned specified that the condition is suspensive. Unless otherwise specified, a fulfilment of the condition does not require a submission of a request for another substantial modification.’

(b) in paragraph 2, the second subparagraph, is replaced by the following:

‘Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds, provided that the consideration was raised during the process pursuant to Article 18(4) and it considers that it was not sufficiently addressed:

(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

(b) infringement of its national law as referred to in Article 90.’

(23) Article 25 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) in the first subparagraph, point (e) is replaced by the following:

‘(e) justification as to why the clinical trial is a minimal-intervention or low-intervention clinical trial, in cases where this is claimed by the sponsor.’;

(ii) the second subparagraph is replaced by the following:

‘The list of required documentation and information for Part I is set out in Part I of Annex I. The list of required documentation for Part II is set out in Part II of Annex I.’;

(b) the following paragraphs 1a, 1b and 1c are inserted:

‘1a. The requirements for Part I may be adapted for minimal-intervention or low-intervention clinical trials **through delegated acts in accordance Article 27, point (c).**’

‘1b. The sponsor shall use harmonised templates, where such templates are available **adopted by the Commission in accordance with paragraph 1c,** for the submission of documents for Part II of the application dossier necessary for the authorisation of the clinical trial, in accordance with the requirements ~~described in~~ **of** Article 7(1) of this Regulation.

1c. To draw up and update, when necessary, harmonised templates to be used by sponsors, the Commission shall be empowered to adopt implementing acts in accordance with Article 88. The harmonised templates may include standardised sections for documents referred to in ~~Article 7(2)~~ **Article 7(1)** and in Annex I.’

(c) the following paragraph 2a is inserted:

‘2a. The requirements referred to in paragraph 2 may be adapted for minimal-intervention and low-intervention clinical trials **in accordance with Article 27, point (c).**’

(d) the following paragraphs 8 and 9 are added:

- ‘8. An application dossier for an authorisation of a clinical trial or for an authorisation of a substantial modification may ~~rely on~~ **incorporate** ~~on~~ health data accessed under Chapter IV of Regulation (EU) 2025/327 of the European Parliament and of the Council*
9. National competent authorities and ethics committees shall ensure that the persons validating or assessing the initial application and substantial modification requests ~~use~~ only documents which are listed in Part I and Part II of Annex I and Annex II.’

* Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (OJ L, 2025/327, 5.3.2025. ELI: <http://data.europa.eu/eli/reg/2025/327/oj>).

(23a) Article 27 is replaced with the following:

Article 27

Delegated acts to amend Annexes I and II

The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in respect of amending Annexes I and II in order to:

- (a) **adapt them to technical, scientific and regulatory progress;**
- (b) **take account of international regulatory developments in which the Union or the Member States are involved, in the field of clinical trials or;**

- (c) to specify adapted requirements for minimal-intervention or low-intervention clinical trials as provided for in this Regulation. Such adapted requirements shall:
- (i) reflect a risk-based approach that takes into account the level of assurance already established for authorised medicinal products used as investigational medicinal products;
 - (ii) avoid the need for the submission or review of data that has already been assessed as part of the marketing authorisation;
 - (iii) take into account the established safety reporting and oversight mechanisms for such products;
 - (iv) ensure that the necessary information is provided to allow appropriate consideration of any intended use of the investigational medicinal products outside of the terms of their marketing authorisations or any deviations from normal clinical practice
 - (v) maintain an equivalent level of overall assurance regarding the protection and safety of subjects as well as ensuring data reliability and robustness.

(24) the following Chapters IVa and IVb are inserted:

‘Chapter IVa

INVESTIGATIONAL MEDICINAL PRODUCT CORE DOSSIER

Article 27a.

Establishment of an investigational medicinal product core dossier

1. At the time of submission of a clinical trial application referred to in Articles 5 and 11 the sponsor may request through the EU portal the establishment of an investigational medicinal product core dossiers. That clinical trial application will be regarded as the 'initial clinical trial' for the investigational medicinal product core dossier.
To this end, the sponsor, shall provide data and information referred to in point (Ga) of Part I of Annex I.

2. The sponsor shall submit the request for the establishment of the investigational medicinal product core dossier to all Member States concerned of the initial **clinical trial**, **the sponsor may also submit the request to any other Member State to which the sponsor plans to submit other clinical trial applications using the same investigational medicinal product**. **These Member States collectively will be considered to be core dossier competent Member States**. ~~The sponsor may extend this request to other Member States than the Member States concerned.~~ The reporting Member State of the initial clinical trial **in which the sponsor has requested to establish the investigational medicinal product core dossier** shall become the **core dossier** depositary Member State. **The sponsor shall submit an investigational medicinal product core dossier overview with the request, describing the scope of the intended use of the investigational medicinal product in the clinical trial including the information described in paragraph (54a) of point (Ga) of Part I of Annex I and a version number**.
3. The **core dossier** depositary Member State shall verify the completeness and suitability of the **investigational medicinal product** core dossier for the purposes of the initial clinical trial. **The assessment of the investigational medicinal product core dossier will follow the same procedures and timelines applicable to the initial clinical trial but will constitute a parallel assessment**.

At the latest, by the time when the conclusion of the assessment of Part I is ~~due in accordance with Article 6(3)~~ **finalised in accordance with Article 6(8)**, the **core dossier** depositary Member State shall notify the sponsor and the other core dossier competent Member States through the EU portal of the establishment of the investigational medicinal products core dossier where the assessment is positive. **The investigational medicinal product core dossier overview and assessment reports relevant to the investigational medicinal product core dossier will be made available to all Member States via the EU portal**.

4. The investigational **medicinal** product core dossier shall be relied upon by the reporting Member State and the Member States concerned in the process of authorising the initial clinical trial referred to in paragraph 1.
5. Once established, the investigational medicinal product core dossier shall be referred to in all subsequent applications concerning the clinical trial in the context of which the investigational medicinal products core dossier was established and any other corresponding clinical trial **submitted by the same sponsor. Where the sponsor of a subsequent clinical trial differs from the sponsor of the initial clinical trial, a letter of access may be submitted by the sponsor of the initial clinical trial to allow the investigational medicinal product core dossier to be used in the subsequent clinical trial. A change in the sponsor responsible for the core dossier shall not affect the validity of any existing authorised clinical trial that uses the investigational medicinal product core dossier.**

Article 27b

Maintenance and changes of the investigational medicinal products core dossier

1. The sponsor shall keep the investigational medicinal product core dossier updated and shall review it at least once per year. When the sponsor identifies a necessity to update the investigational **medicinal** products core dossier, paragraph 2 applies.
2. When ~~new information, relevant to maintain the suitability and completeness of an established investigational product core dossier becomes known to the sponsor,~~ **the core dossier depositary Member State or a reporting Member State for a corresponding clinical trial, identify the need to make a change to the investigational medicinal product core dossier,** the sponsor shall submit to the **core dossier** depositary Member State, through the EU portal, a request for a change of the investigational medicinal product core dossier.

The core dossier depositary Member State shall take the lead role in the assessment of the change, with the involvement of the core dossier competent Member States (including other reporting Member States of the corresponding clinical trials) in the procedure.

As part of the assessment, the depositary core dossier Member State shall assess whether the investigational medicinal product core dossier, as amended, remains adequate and complete for the corresponding clinical trials, in accordance with the applicable requirements set out in Annex I Ga.

In the event that the change is acceptable, an updated investigational medicinal product core dossier overview along with the relevant assessment reports will be made available to all Member States via the EU portal.

The sponsor and any other sponsors for clinical trials in which the investigational medicinal product is used, will update the EU database within 7 days of implementation of any changes to the investigational medicinal product core dossier which are relevant for the supervision of the clinical trial and the procedure described in Article 81(9) will apply.

3. In case of a new application for an authorisation of a new corresponding clinical trial, the reporting Member State of that clinical trial together with the **core dossier** depositary Member State shall assess the suitability of the investigational **medicinal** product core dossier for the purpose of the authorisation of the trial application, that is;
 - (a) whether the investigational **medicinal** product core dossier is complete as regards the information on the characteristics and knowledge about the investigational medicinal products;
 - (b) if appropriate, the compliance with the requirements concerning the manufacturing and import of investigational medicinal products set out in Chapter IX;
 - (c) whether the IMPD is adequate and complete for the scope of use as proposed by the sponsor in the application in accordance point Ga, Part I of Annex I.

The reporting Member State of the corresponding clinical trial shall communicate the results of its assessment to the depositary Member State.

Where the new corresponding clinical trial involves changes to the previous scope of authorised use of the investigational medicinal product in a clinical trial, the core dossier depositary Member State will assess whether the changes have any impact on the suitability of the investigational medicinal product core dossier, and provide its opinion to the reporting Member State for inclusion in its draft assessment report for the new corresponding clinical trial application.

When the assessment of Part I is finalised in accordance with Article 6(8), the reporting Member State will inform the core dossier depositary Member State of the conclusion of the assessment of the clinical trial application. The investigational medicinal product core dossier overview shall reflect any changes in the scope of the authorised use of the investigational medicinal product in a clinical trial and any new core dossier competent Member States added via the clinical trial procedure. The updated overview and any updated assessment reports relevant to the investigational medicinal product core dossier will be made available to all Member States via the EU portal.

If the investigational product core dossier does not contain all the information necessary for the authorisation of the clinical trial, the reporting Member State may request the sponsor to change the investigational product core dossier.

The sponsor shall in such situations request a change of the investigational medicinal product core dossier in accordance with paragraph 2.

4. ~~After receiving the request for a change to the core dossier, independently of whether a change is submitted in the context of an assessment of an application related to a corresponding clinical trial or independently, the depositary Member State shall verify whether the core dossier, once changed, will continue to fulfil the requirements listed in paragraph 3 points (a), (b) and (c). The Member State concerned with the core dossier shall not duplicate the assessment of the depositary Member State. The depositary Member State may consult the Member State concerned as appropriate.~~

- ~~5.~~ **4.** If a request for a core dossier change is submitted in the context of an ongoing assessment related to a corresponding clinical trial, the timeline for change of the core dossier shall allow for timely approval of the clinical trial, **and if necessary and appropriate, the clinical trial application may be approved subject to a condition requiring approval of a change to the investigational medicinal product core dossier.**
- ~~6.~~ The sponsor shall assess whether a change to the investigational product core dossier makes it necessary to submit a substantial modification in corresponding clinical trials that are ongoing.

Article 27c

Procedural aspects related to the establishment and maintenance of the investigational medicinal products core dossier

The Commission shall set out the detailed rules governing the submission of a request for the establishment of an investigational product core dossier, its assessment and maintenance by means of implementing acts, including the rules for cooperation between the core dossier competent Member States and the change of **core dossier** depositary Member State. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88.”

REGULATORY SANDBOXES AND USE OF AI

Article 27d

Regulatory sandbox

1. The Commission may establish and operate a regulatory sandbox at Union level, ~~that provides a controlled and time limited framework to enable, under real world conditions, the testing of innovative approaches in clinical trials to which the full application of certain requirements of this Regulation is not possible or appropriate and which therefore may require adaptations.~~ **The regulatory sandbox may allow for targeted temporary exemptions from the requirements of this Regulation which are necessary due to innovative approaches in the authorisation and conduct of a clinical trial or due to the specificity of the investigational medicinal product contributing to at least one of the objectives set out in paragraph 4, point (b). The targeted temporary exemptions may entail adapted, enhanced, waived or deferred requirements. Each exemption shall be limited to what is strictly necessary to attain the objectives pursued, duly justified and specified in the conditions to the sandbox.**

Such temporary exemptions shall not affect the safety, well-being, and fundamental rights of clinical trial subjects, data robustness or integrity of the clinical trial.

2. The regulatory sandbox under this Regulation may encompass **innovative** approaches to the authorisation and conduct of the clinical trials and where appropriate, ~~maybe~~ **may** be implemented in coordination and synergies with the regulatory sandboxes established pursuant to Regulation (EU) 2024/1689. with ~~full~~ involvement of competent authorities supervising the sandbox under Regulation (EU) 2024/1689-**as appropriate** and in accordance with the relevant procedures and rules for participating in those AI regulatory sandboxes.

- 2a. Where, based on available scientific evidence, including consideration of any requests for the establishment of a regulatory sandbox received from Member States or sponsors, the Clinical Trials Coordination and Advisory Group (CTAG) considers it could be appropriate to establish a regulatory sandbox under this Regulation, or upon request of the Commission, the CTAG shall provide a recommendation to the Commission. The recommendation shall describe, inter alia, the scope and objectives of the regulatory sandbox and include a recommended regulatory sandbox plan referred to in paragraph 3.**
3. The activities within a regulatory sandbox shall take place pursuant to a specific plan **developed by the CTAG and subject to approval by the Commission**, for eligible clinical trials, which ~~may~~ **shall** be conducted under enhanced regulatory oversight of the Member States concerned. The plan shall clearly identify the requirements of this Regulation that are temporarily adapted or **exempted** ~~derogated~~ from in the sandbox and that may relate to, as necessary, to source data and documentation requirements, recruitment and informed consent procedures, monitoring and reporting requirements, trial design rules, investigational medicines handling rules, safety reporting rules, site requirements. The plan shall also identify, **inter alia**, the roles and responsibilities of sponsors, investigators, and manufacturers. **and shall set out clinical, scientific and regulatory justification for the sandbox.**
4. A regulatory sandbox may be established only if **all of** the following conditions are met:
- (a) it is not possible to authorise or conduct a clinical trial in full compliance with the requirements of this Regulation due to innovative approaches in the clinical trial or due to the ~~specificity~~ **scientific or technical characteristics** of the investigational medicinal product;

- (b) enabling the approaches and characteristics referred to in point (a) ~~are~~ is expected to contribute to at least one of the following objectives:
- (i) increasing the value and robustness of the data generated in the trial
 - (ii) considerably decreasing clinical trial length, and increasing the efficiency of the clinical trial;
 - (iii) enabling new technologies and approaches in the development of medicinal products that have the potential to positively and distinctively contribute to better prevention, diagnosis, and treatment, as well as increase adherence to treatment plans or improve the efficiency of the provision of health care;
- (c) the sandbox provides safeguards to ensure the safety, well-being, and respect for the fundamental rights of clinical trial participants, data robustness, and maintained integrity of the clinical trials within the sandbox.
5. The regulatory sandbox shall not affect the supervisory or corrective powers of the Member States concerned and shall operate under the direct supervision of the competent authorities in the Member State concerned for activities that take place on its territory.
- 5a. Participants in the regulatory sandbox, including the sponsor, shall remain liable under applicable Union and national law for any harm inflicted on third parties as a result of the clinical trial taking place under the regulatory sandbox.**
6. ~~Before setting up a sandbox, the Commission shall request an opinion of the CTAG.~~
7. **Following the receipt and consideration of a recommendation from the CTAG as referred to in paragraph 2,** ~~t~~The Commission may establish a regulatory sandbox by means of implementing acts, ~~after taking into consideration opinions referred to in paragraph 6.~~ Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88.

7a. A decision establishing a regulatory sandbox under paragraph 7 shall be limited in time and shall lay down detailed conditions for its implementation. It shall include:

- (a) the final regulatory sandbox plan, taking into account the recommended regulatory sandbox plan of the CTAG, specifying the specific requirements and the targeted temporary exemptions, in accordance with paragraph 3 of this Article, to the requirements of this Regulation;**
- (b) the duration of the regulatory sandbox and its expiry taking into account the time needed for development of the investigational medicinal products and the conduct of the clinical trials within the scope of the sandbox.**

8. Notwithstanding other reporting requirements provided for under this Regulation, during the operation of a regulatory sandbox, sponsors or Member States shall inform the CTAG of any information which might entail the amendment of the regulatory sandbox or of any concerns relating to the health, safety or fundamental rights of clinical trial participants or the integrity and robustness of clinical trial data. ~~Member States shall notify the Commission of any risk to health and safety or fundamental rights or integrity and robustness of data identified during the operation of a sandbox.~~ In these cases, the Commission may, by means of implementing acts, **amend**, suspend or revoke a regulatory sandbox.

~~8.~~ **9.** Without prejudice to Article 114(1) of [Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final*], where in the context of a regulatory sandbox under Article 113 of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final*] is considered that new regulatory approaches in clinical trial are necessary for the product development, the Commission may consider to establish a regulatory sandbox under this Regulation to complement the regulatory sandbox established under Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final*].

Article 27e
Use of Artificial Intelligence in Clinical Trials

1. For those clinical trials where the sponsor plans to use AI models or systems, the sponsor shall evaluate the benefits and risks related to patient safety and data robustness of the use of the AI in the context of a specific clinical trial for a specific purpose taking into account the guidelines **referred to** ~~laid down~~ in Article 37**31** of Regulation [...] [Biotech Act].
2. The sponsor shall provide information in the protocol on the specific purpose of the use of AI models or systems and the description of the process in the context of the specific clinical trial. **as per the conditions set in Annex I.**
3. When the investigation of a medicinal product in a clinical trial is combined with a performance study of an AI in vitro diagnostic medical device or a clinical investigation of an AI medical device, the provisions of Article 14**c** on coordinated assessment for authorising combined studies shall apply.
4. In cooperation with the CTAG and, where appropriate, the Medical Device Coordination Group, the Artificial Intelligence Board, the Agency shall develop guidelines referred to in paragraph 1 of this Article.

**** Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193final**

(25) Article 28 is amended as follows:

(a) paragraph 2 is deleted

~~(b) In paragraph 3, the last sentence is deleted~~

(b) Article 28(3) is replaced by the following

‘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 trial at any time by revoking his or her informed consent. Without prejudice to Regulation 2016/679, 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.’

(26) in Article 29(1), the following subparagraph is added:

‘The communication in the context of an interview between the **appropriately qualified member of the** ~~investigating team~~ **investigating team referred to in paragraph 2(c)** and the subject or the **appropriately qualified member of** the ~~investigating team~~ **referred to in paragraph 2(c)** and the subject and ~~its~~ **his or her** legally designated representative, as applicable, may be done remotely through use of **validated** electronic means. The record of the informed consent procedure may have an electronic form and shall be signed relying on electronic identification means complying with Regulation (EU) No 910/2014 of the European Parliament and of the Council* or the equivalent standards. **The sponsor shall ensure that the appropriately qualified member of the investigating team and the subject are given the option to have the informed consent interview conducted on site and the record of the informed consent procedure in a non-electronic format if requested.**

(26a) In Article 29(2), the following point is inserted:

- (v) **their rights as they relate to data protection, as set out in Article 93.**

* Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC, OJ L 257, 28.8.2014.ELI: <http://data.europa.eu/eli/reg/2014/910/oj>.”

- (27) in Article 30(3), point (c) is replaced by the following:

‘(c) the clinical trial is a minimal-intervention clinical trial;’

- ~~(28) in Article 31(1), point (e) is deleted:~~

- ~~(29) in Article 32 (1), point (e) is deleted;~~

- (30) in Article 33, the following second paragraph is inserted:

‘Women who become pregnant or begin breastfeeding while participating in a clinical trial shall not be automatically excluded from participation in the clinical trial.

Their continued participation shall be subject to a careful assessment of the associated risks and benefits in accordance with the inclusion and exclusion criteria set out in the trial protocol. Where continued participation is confirmed in accordance with the trial protocol, an updated informed consent form shall be signed, and any additional safeguards and tailored monitoring procedures specified in the protocol shall be implemented.

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(30a) in Article 36, paragraph 3 is amended as follows:

3. **The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU portal.**

That notification shall confirm the number of participants recruited in the clinical trial in the Member State and shall be made within 15 days from the end of recruitment of subjects. In case of re-start of recruitment, paragraph 1 shall apply.

(31) in Article 41, the following paragraph 5 is added:

- '5. Reporting requirements of adverse events and serious adverse events for minimal-intervention and low-intervention clinical trials shall be simplified by applying a risk-based approach **that takes into account the established knowledge of the medicinal product(s), relevant pharmacovigilance requirements and their safety profile within the intended target population and in the proposed setting.** Any such adaptation should be clearly stated and justified in the protocol by the sponsor.

(32) in Article 48, point (a) is replaced by the following:

‘(a) whether the clinical trial is a minimal-intervention or low-intervention clinical trial;’:

(33) the following Article 50a is inserted:

'Article 50a.

Delivery at a distance of investigational **medicinal products** and auxiliary medicinal products ~~through a dispensing pharmacy, an authorised person or directly to the subject~~

~~When~~**Where appropriately** justified in the **authorised** protocol, the delivery of investigational medicinal products and auxiliary medicinal products to the ~~clinical trials~~ subjects may be ensured at a distance under the supervision of the investigator, **through persons authorised under the national law of the Member State concerned to supply such medicinal products to clinical trial subjects.**

Member States may also allow the delivery at a distance of investigational medicinal products and auxiliary medicinal products to take place directly to place of residence of the subject, provided that the arrangements are appropriately justified in the protocol.

Member States shall establish rules governing the delivery at a distance, including the standards regarding the handling, storage, transport, traceability and record-keeping and the modalities for such delivery, taking into consideration as appropriate the guidelines referred to in paragraph 2.

~~In case of a minimal intervention and a low intervention clinical trial, the distribution of the investigational medicinal products can be ensured in a Member State where the clinical trial has been authorised, under the responsibility of the investigator, through the dispensing pharmacies or by persons authorised to supply medicinal products to the subject.~~

The authorised protocol and investigator's brochure shall describe the arrangements for the direct delivery delivery at a distance to subjects or through dispensing pharmacies or persons authorised to supply to the patients, including the roles and responsibilities of all parties involved and procedures for secure handling, storage, traceability and record keeping.

The direct delivery at a distance to subjects shall comply with the national law of the Member State and with the conditions laid down in this Regulation. ~~guidelines referred to in paragraph 1 of Article 63a.:~~

2. The inspection working groups referred to in Article 142, point (k), of Regulation (EU) .../... [reference to be added after adoption COM(2023)193final], in agreement with the Commission, may draw up guidelines on general principles and common standards applicable to the delivery at a distance of investigational medicinal products and auxiliary medicinal products to clinical trial subjects and revise them as necessary to take account of technical and scientific progress.

(34) in Article 51(1), first subparagraph is replaced by the following:

‘Investigational medicinal products shall be traceable. They shall be stored, returned and/or destroyed as appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial, in particular, taking into account whether the investigational medicinal product is an authorised investigational medicinal product, and whether the clinical trial is a minimal-intervention or low-intervention clinical trial.’;

(35) in Article 53(2), the first sentence is replaced by the following:

‘The sponsor shall submit to the Member States concerned, through the EU portal, inspection reports of third country authorities concerning the clinical trial, ~~and relevant to subject safety.~~’

(36) in Article 57, the first subparagraph is replaced by the following:

‘The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a minimal-intervention or low-intervention clinical trial. **The clinical trial master file shall be readily available, and directly accessible upon request, to the Member States.**

(37) Article 61 is amended as follows:

(a) paragraph 6 is replaced by the following:

‘6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial while taking into account the guidelines referred to in paragraph 7. They shall subject the processes to regular inspections.’;

(b) the following paragraph 7 is added:

- ‘7. The inspection working groups referred to in Article 142, point (k) of Regulation (EU) .../... of the European Parliament and the Council [*reference to be added after adoption cf. COM(2023) 193 final*]*, in agreement with the Commission, may draw up guidelines on general principles applicable to the processes set out in paragraph 5, including for auxiliary medicinal products, and revise them as necessary in order to take account of technical and scientific progress.

*Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193final.’

(38) in Article 63, paragraph 4 is replaced by the following:

4. The Member States shall ensure compliance with the requirements of this Article by means of inspections. Articles 188, with exception of its paragraph 3**(b)** and 4**(b)**, and 189 of Directive (EU) .../... [*reference to be added after adoption cf. COM(2023) 192 final*]* and article 52 of Regulation (EU) .../... of the European Parliament and the Council [*reference to be added after adoption cf. COM(2023) 193 final*]** apply *mutatis mutandis*

* Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC COM/2023/192final

** Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193final'

(39) the following Article 63a is inserted:

'Article 63a

Distribution

1. The distribution of investigational medicinal **products** shall comply with standards that shall ensure **that** their quality and integrity **is maintained throughout the supply chain**. The Commission shall adopt delegated acts supplementing this Regulation by determining the standards of good distribution practices for investigational and auxiliary medicinal products taking into account the input of the inspection working groups referred to in Article 142, point (k) of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final], and update them if necessary to take account of scientific and technical progress.
2. Where the competent authority of the Member State considers it necessary, in particular where there are grounds for suspecting non-compliance with the requirements of this Article, it may carry out inspections to verify the compliance.
3. Arrangements for inspections referred to in Article 63(1) apply mutatis mutandis to inspections of good distribution practices for investigational and auxiliary medicinal products.';

(40) in Article 76, paragraph 3 is replaced by the following:

- ‘3. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for minimal or low-intervention clinical trials, if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.’;

(41) Article 78 is amended as follows:

- (a) paragraph 1 is replaced by the following:

- ’1. The national competent authorities shall organize inspections in order to supervise compliance with this Regulation.

Member States shall appoint inspectors to perform the inspections in order to supervise compliance with this Regulation. **They shall ensure that those inspectors are adequately qualified and trained.**

The competent authority of the Member State **concerned** shall have in place a system of supervision that shall include the following measures:

- (a) announced, and where appropriate, unannounced on-site inspections;
- (b) remote inspections conducted where justified;
- (c) compliance control;
- (d) the effective follow up of the measures referred to in points (a), (b) and (c).’;

(b) **p**aragraph 6 is replaced by the following:

“6. Following an inspection, the Member State under whose responsibility the inspection has been conducted, shall draw up an inspection report. That Member State shall make the inspection report available to the inspected entity and the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal within 90 days **of an inspection being carried out** after ~~conducting the the inspection~~.”;

(c) paragraphs 8, 9 and 10 are added:

- ‘8. Upon a request by one or more competent authorities of the Member State **responsible for the inspection**, the inspection referred to in paragraph 1 may be carried out jointly by **inspectors from that Member State**, ~~the~~ inspectors from **one or more than one other** Member States, and, **where requested by the competent authority of the Member State responsible for the inspection**, ~~the~~ inspectors from the Agency.
9. **A** Member States **responsible for an inspection** may **request to** delegate to another Member State or the Agency the conduct of a good clinical practice inspection. The Commission may adopt a delegated act in accordance with Article 89 to supplement this Regulation by laying down the procedures applicable to joint inspections and delegation of inspections.
10. This Article does not apply to the good manufacturing practice inspections and the good distribution practices inspections related to application of this Regulation, in accordance with Articles 63 and 63a respectively.’;

(42) Article 79 is replaced by the following:

'Article 79.

Union controls

1. The Commission may conduct controls in order to verify:
 - (a) whether the Member States correctly supervise compliance with this Regulation;
 - (b) whether **the** regulatory system applicable to clinical trials conducted outside the Union ensures that the clinical trials referencesd in the applications for marketing authorisations in the Union are designed, implemented and reported ~~on what~~ **in accordance with** good clinical practice and ethical principles ~~are concerned, on the basis of~~ **and based on** principles that are equivalent to **those** ~~the ones~~ established in this Regulation;
 - ~~(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied with.~~
- 1a. In order to perform the Union controls referred to in paragraph (1) point (a), the Commission may verify **the national system of oversight and confirm** whether competent authorities and ethics committees have in place adequate and effective mechanisms to ensure compliance with this Regulation as regards in particular the requirements related to:
 - (a) validation of ~~the~~ clinical trial applicationss as referred to in Articles 5(3)(**b**), 17(2) and Article 20;
 - (b) scientific and ethical review as referred to in Article 4, Articles 6(1), 7(1), 8, 9 and 10, assessment of substantial modifications as referred to in Articles 17 to 22, safety assessment referred to in Article 44;
 - (c) communication and coordination with other Member States as referred to in Articles 5 to 8, Article 14, Article 17 to 19, Article 22 and 23;
 - (d) manufacturing and import of investigational medicinal products as referred to in Articles 61 and 63(4);
 - (e) application of corrective measures and penalties as referred to in Article 77 and 94;
 - (f) conduct **of** inspections as referred to in Articles 78, 63 and 63a.

2. The Commission shall organise the controls referred to in paragraph 1 in cooperation with the ~~national authorities~~ **competent authorities and/or ethics committees** and shall carry them out in a manner that avoids unnecessary administrative burden.
3. When performing the controls referred to in paragraph 1, the Commission shall consult the relevant best practices.
4. The Commission, in carrying out the controls referred to in paragraph 1, may be supported by experts from the competent authorities or ethics committees.
5. Following each control, the Commission shall:
 - (a) prepare a draft report on the findings and, where appropriate, include recommendations addressing the shortcomings identified;
 - (b) send a copy of the draft report referred to in point (a) to the ~~clinical trials national authority~~ **competent authorities and/or ethics committees** concerned for its comments;
 - (c) take the comments referred to in point (b) into account in preparing the final report; and
 - (d) submit the final report through the EU portal.”;

(43) the following Article 79a is inserted:

'Article 79a.

Obligations as regards Union controls

Member States shall cooperate with the Commission in respect of the performance of the Union controls referred to in Article 79 (1). In particular, they shall:

- (a) ensure that the necessary technical assistance and the relevant documentation are provided to the Commission, upon justified request, ~~is being provided to the Commission as well as~~ and provide any other reasonable support that the Commission requests to enable it to perform controls efficiently and effectively, including facilitating access to all premises or any part thereof, to personnel (interviews) and data, including IT systems of the competent authority that is justified and strictly relevant for the execution of their duties.
- (b) take appropriate follow-up measures to remedy the shortcomings identified through those Commission controls;'

(44) Article 81 is amended as follows:

(a) paragraph 2 is replaced by the following:

The EU database shall be established to enable cooperation between the competent authorities of the Member States concerned to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable communication between sponsors and Member States concerned and reporting Member State as appropriate for the purpose of swift regulatory procedures. It shall enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. It shall also enable citizens of the Union to have **timely** access to **accurate, complete and coherent** clinical information about medicinal products, **presented in language that is clear and accessible**. To this end all data held in the EU database shall be in an easily searchable format, all related data shall be grouped together by way of the EU trial number, and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency.’;

(b) paragraph 9 is replaced by the following:

9. **When introducing changes to clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial, the sponsor shall update the relevant information in the EU database within 7 days of implementation of the changes.** ~~The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial.~~ **Where the authorisation of a clinical trial is subject to a condition which requires the EU portal to be updated to satisfy the condition, the condition will not be considered to be fulfilled until the sponsor has updated the EU portal.** ~~The sponsor shall also update the EU portal to satisfy the condition to which an authorisation decision is subject to.~~
- The reporting Member State or the Member State concerned may review such updates within 30 days of submission, and where considered necessary, require the sponsor to take corrective measures in relation to the changes. Such corrective measures could include a requirement to submit a substantial modification where the Member State considers that the change(s) made require a substantial modification. The sponsor will address the corrective measures within the timeframe specified by the Member State.** ~~An update may trigger a corrective measure from the reporting Member State or the Member State concerned requiring from the sponsor to submit a substantial modification concerning this change. The Member State concerned may issue such corrective measure within 7 days from the date of the update. The sponsor shall submit the substantial modification within period defined in the corrective measure by the Member State.~~

(c) the following paragraph 11 is inserted:

11. The EU database shall serve as the central repository of information and documents submitted under this Regulation. Without prejudice to obligations on the sponsor and the investigator regarding the trial master file, documents submitted to the EU database shall be considered as being archived in accordance with this Regulation.

(45) Article 83 is replaced by the following:

‘Article 83.

Competent authorities and ethics committees

1. Member States shall designate one national contact point to **facilitate** ~~which they confer responsibility for~~ the implementation and practical application of this Regulation. The Commission shall publish a list of national contact points. **Each Member State shall communicate the contact point referred to in paragraph 1 to the Commission.**
2. ~~Each Member State shall communicate the contact point referred to in paragraph 1 to the Commission.~~ Member States shall ensure that competent authorities and ethics committees:
 - (a) have the necessary powers to perform all the necessary regulatory actions and inspections, pursuant to this Regulation.
 - (b) have, or have access to, a sufficient number of suitably qualified and experienced personnel, human and financial resources, operational capacity, and expertise, including technical expertise, for the effective and efficient performance of their tasks they have been made responsible for pursuant to this Regulation.’;

(46) the following Article 83a is inserted:

'Article 83a.

Communication and coordination between competent authorities and between ethics committees

1. Where more than one competent authority and ethics committee are responsible for performing regulatory activities or inspections in a Member State for the purpose of applying this Regulation, Member States shall ensure efficient and effective coordination among all the competent authorities and ethics committees concerned in order to guarantee the consistency and effectiveness of the regulatory activities or inspections performed on their territory. **Such coordination shall include oversight of combined studies.**
- ~~2. Within those Member States, the competent authorities shall cooperate with each other. They shall communicate information to each other for the effective implementation of the regulatory activities and inspections provided for in this Regulation.';~~

(47) Article 85 is replaced by the following:

'Article 85.

Clinical Trials Coordination and Advisory Group

1. A Clinical Trials Coordination and Advisory Group (CTAG) is hereby established.

2. Each Member State shall appoint to the CTAG, ~~for a three-year term which may be renewed once~~, one member and one alternate each with expertise in the field of clinical trials. The members of the CTAG shall be chosen for their competence and experience in the field of clinical trials. They shall represent the views of their Member State ~~competent national authorities and the ethics committees of the Member States~~. The names and affiliations of members and alternates shall be made public by the Commission. The alternates shall represent and vote for the members in their absence.
3. For the purpose of the fulfilment of their tasks, CTAG members shall be able to rely on the contribution of experts from national competent authorities and ethics committees. These experts shall participate in CTAG meetings where relevant.
4. The CTAG shall use its best endeavours to reach consensus. If such consensus cannot be reached, the CTAG shall decide by a majority of its members. Members with diverging positions may request that their position and the grounds on which they are based are recorded.
5. The CTAG shall ~~in particular~~ have the following tasks:
 - (a) to support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation
 - (b) to assist the Commission in providing the support referred to in the second paragraph of Article 84;
 - (c) to prepare recommendations on criteria regarding the selection of a reporting Member State and a core dossier depository Member State which facilitate an equitable distribution of these roles while ensuring the availability of appropriate expertise to review the applications;
 - (d) to provide strategic steering on a common approach for the application of this Regulation and on the support of the clinical trials ecosystem in the Union;
 - (e) to contribute to the development of guidance aiming to ensure effective and harmonised implementation of this Regulation.

- (f) to contribute to the development of guidelines on the use of the artificial intelligence models and systems in clinical trials in accordance with Article [xx] Regulation (EU) .../... [European Biotech Act]*;
- (g) to provide advice, either of its own initiative or at the request of the Commission, in the assessment of any issue related to the implementation of this Regulation;
- (h) to contribute to harmonised administrative practice with regard to clinical trials in the Member States;
- (i) to provide a recommendation ~~before setting up~~ **on the establishment of a** regulatory sandbox
- (j) to conduct any other task that may be necessary to support the implementation of this regulation**

6. The CTAG shall be **co**-chaired by a representative of the Commission **and a representative of a Member State elected by and from the members of the CTAG.**
The **Commission chair** shall not take part in votes of the CTAG.
7. The CTAG may issue recommendations and opinions on matters related to clinical trials and shall endorse any guidance related to the application of this Regulation. The Commission shall publish the guidelines endorsed by the CTAG.
8. The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State. Any item of the agenda of the meeting shall be placed at the request of the Commission or a Member State.
9. The secretariat shall be provided by the Commission.
10. The CTAG shall draw up its rules of procedure. The rules of procedure shall be made public.

(47a) Article 89 is replaced by the following:

'Article 89

Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.
2. The power to adopt delegated acts referred to in Articles 14b, 14c, 27, 39, 45, 63(1), 63a, 70 and 78 shall be conferred on the Commission for a period of five years from the date referred to in the second paragraph of Article 99. The Commission shall draw up a report in respect of the delegated powers not later than six months before the end of the five year period. The delegation of powers shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.
3. The delegation of power referred to in Articles 14b, 14c, 27, 39, 45, 63(1), 63a, 70 and 78 may be revoked at any time by the European Parliament or by the Council. A decision of revocation shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the Official Journal of the European Union or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.
4. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.
5. A delegated act adopted pursuant to Articles 14b, 14c, 27, 39, 45, 63(1), 63a, 70 and 78 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of two months from notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or the Council.'

(48) Article 93 is replaced by the following:

'Article 93

Data protection

1. When carrying out their tasks pursuant to this Regulation, sponsors are required to process personal data, including genetic data or data concerning health **where such processing is necessary** for the following purposes:
 - (a) for the submission of applications in accordance with Articles 5, 11, 14 and 16;
 - (b) to perform research activities in the context of a clinical trial in accordance with the protocol as authorised by the national competent authorities in accordance with point D, Part I of Annex I;
 - (c) to perform safety operations and reporting in accordance with Articles 41 to 43 and 52 to 54;
 - (d) to record, process, handle and store information in accordance with Article 56;
 - (e) to perform archiving in accordance with Article 58;
 - (f) to submit to the EU portal the summary of the results of the clinical trial, the lay summary, the clinical study report and, where applicable, raw data, in accordance with Article 37(4).
 - (g) to adequately monitor the conduct of a clinical trials in accordance with Article 48.**
- “2. When carrying out their tasks pursuant to this Regulation, **the site in which the investigator operates the clinical trial is** ~~are~~ required to process personal data, including genetic data or data concerning health **where such processing is necessary** for the following purposes:
 - (a) to perform research activities in the context of a clinical trial in accordance with the protocol as authorised by the national competent authorities in accordance with point D, Part I, Annex I;

- (b) to perform safety reporting in accordance with Articles 41 and 54;
- (c) to record, process, handle and store information in accordance with Article 56;
- (d) to perform archiving in accordance with Article 58.

(e) to adequately monitor the conduct of a clinical trial.

3. **The sponsor and the site in which the investigator operates the clinical trial**

~~Sponsors and investigators~~ shall make available personal data, including genetic data or data concerning health:

- (a) to the competent authorities of the Member States, **to the extent necessary**, for the purposes of oversight activities, including inspections, in accordance with Article 78 and
- (b) to the Commission, **to the extent necessary**, for the purposes of controls, in accordance with Article 79.

4. For the processing assessment leading to the authorisation of clinical trial applications and operations referred to in this Article, **the site in which the investigator operates the clinical trial is a** ~~sponsors and investigators~~ controllers within the meaning of Article 4(7) of Regulation (EU) 2016/679.

For the processing of personal data related to the assessment leading to the authorisation of a clinical trial application and related to the operations referred to in paragraph 1, points (b) to (g) and paragraph 3 in this Article, the sponsor shall be the controller within the meaning of Article 4(7), of Regulation (EU) 2016/679.

For the processing of personal data related to the operations referred to in paragraphs 2, points (a) to (e) and 3 of this Article, the site in which the investigator operates the clinical trial, acting through the investigator and other persons under its authority, shall be the controller within the meaning of Article 4(7) of Regulation (EU) 2016/679.

Co-sponsors as provided for Article 72 of this Regulation shall be regarded as joint controllers.

5. Personal data, including genetic data or data concerning health **contained in the clinical trial master file**, shall be retained as long as required pursuant to Article 58 and in accordance with the conditions laid down therein.
6. Personal data collected and processed in accordance with this Regulation may be further processed by the same controller **where such processing is necessary** for the purposes of other clinical trials conducted under this Regulation, ~~or for scientific research with the aim of protecting public health, improving standard of care and fostering the innovation capacity of European medical research.~~ **Further processing for scientific research purposes shall be permitted only where those purposes are clearly defined, directly related to the medicinal product, disease, condition, treatment, intervention or safety assessment addressed in the authorised protocol, and subject to Regulation (EU) 2016/679, including appropriate safeguards pursuant to Article 89(1) of that Regulation.**
7. By derogation from Article 9(4) of Regulation (EU) 2016/679, Member States may not maintain or introduce further conditions, including limitations, with regard to the processing of personal data, including genetic data or data concerning health in the context of clinical trials carried out in accordance with this Regulation.
8. Processing of personal data referred to in this Article shall be subject to appropriate technical and organisational measures to ensure the protection of the rights and freedoms of **the** data subject. ~~In particular,~~ **The** controller shall obtain informed consent of the subject in accordance with Article 29 of this Regulation.

The controller shall also use of pseudonymisation whenever it is not necessary to process directly identifiable personal data.

The controllers shall also apply confidentiality rules concerning access to records and personal data of subjects and apply further safeguards that are appropriate for a specific clinical trial as requested in point D, Part I of Annex I (ak), **(ak1)**, (al), **(al1)**, (am).

(49) Article 97 is replaced by the following:

“Article 97.

Review

Five years after the **[date of application of the Biotechnology Regulation]** date referred to ~~in Article 99, second subparagraph,~~ and every ~~ten~~ **five** years thereafter, the Commission shall present a report to the European Parliament and to the Council on the application of this Regulation. That report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The report shall also assess progress made by monitoring as ~~a~~ **key performance indicators** the number of additional multinational clinical trials authorised in the Union over the ~~5~~ **five**-year period of the reporting, compared to the average number of such clinical trials authorised per year in the Union as of 2025; **and the number of subjects participating in clinical trials authorised in the Union over the five-year period of the reporting**

The Commission shall, if appropriate, present a legislative proposal based on that report in order to update the provisions set out in this Regulation”

(50) in Article 98, paragraph 1 is replaced by the following:

1. This Regulation, as applicable on [Publication Office: please insert the date of the day before the date of application of Biotechnology Regulation] shall continue to apply to the procedures for authorisation, substantial modification ~~of~~ **or** addition of a Member State concerned of a clinical trial where the request for the authorisation, **substantial modification or addition of a Member State concerned** has been submitted before the date of entry into application as referred in Article 67(3), point (a), of Regulation [...] [European Biotech Act]. **By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial has been submitted before the date referred to in the second paragraph of Article 99 of this regulation pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until three years from that date.**

(51) the following Article 98a is inserted;

'Article 98a.

Development plan for the EU Portal and database

The Agency shall be responsible for reporting, on the development, maintenance and, where relevant, adjustment of the EU portal in terms of timing, budgetary compliance and quality.

This would include a submission, after consulting the Commission, of a revised development plan for **the** EU Portal and database to the Agency's Management Board 1 month after entry into force of Regulation (EU).../... of the European Parliament and of the Council [include reference to Biotech Act proposal].* The development plan shall ensure that all required system functionalities are available by the date of application as defined in Article [...] of Regulation (EU).../...[Biotech Act proposal].

The summary of the development plan with key milestones and timelines [once approved by the Management Board of the Agency] shall be made publicly available at the website of the Agency. **The Agency shall present reports on the functioning of the EU Portal to the Agency's Management Board 12 months and 24 months after entry into force of Regulation (EU).../... of the European Parliament and of the Council [include reference to Biotech Act proposal]. These reports shall include an assessment of the impact of the implementation of the updated system functionalities and their use in the clinical trial procedures outlined in this Regulation taking into account feedback received from users.**

*Biotechnology proposal

(52) Annex I is amended in accordance with Annex **II** to this Regulation

Annexes to Regulation (EU) 536/2014 are amended as follows:

(1) ~~Annex I is replaced by the following:~~ **Annex I is amended as follows:**

‘Annex I

Part I

A. INTRODUCTION AND GENERAL PRINCIPLES

5. (deleted)

B. COVER LETTER

~~The cover letter shall include a summary of the activities that are planned to **be conducted** outside **of the traditional clinical** trial sites, enabled by digital technologies, remote procedures, and alternative delivery models in clinical trials.~~

(fbis) whether the investigational medicinal products consist or contain genetically-modified organism(s) and, where applicable, whether they fall within one or more of the categories listed in Article 4a(1), points (a) to (d), of Regulation (EC) No 1394/2007;

9. The cover letter shall indicate if the clinical trial is considered by the sponsor to be a minimal or low-intervention clinical trial and shall contain a detailed justification thereof.

12a. The cover letter shall ~~include a summary of the~~ **indicate any** activities **(e.g. remote procedures, direct delivery to subjects)** that are planned to **be conducted** outside **of the traditional clinical** trial sites where the investigator operates, ~~enabled by digital technologies, remote procedures, and alternative delivery models in clinical trials.~~

D. PROTOCOL

17. The protocol shall at least include:

(x) a justification for including **or excluding** subjects who are incapable of giving informed consent or other special populations, such as minors **and women who become pregnant or begin breastfeeding while participating in a clinical trial;**

(ak1) a description of specific technical and organisational measures while processing personal data that should be employed, including pseudonymisation, integrity and confidentiality controls, encryption and access restrictions;

(al1) a description of the processing operations, the categories of personal data and the necessity for their processing, the categories of data subjects concerned, the entities to, and the purposes for which the personal data may be disclosed, as well as the retention period for these personal data.

(an) justification of allowing for a direct delivery to subject of an investigational medicinal product(s) **or an auxiliary medicinal product(s);**

(ao) a detailed description of the management of **any proposed direct delivery to the subject of** investigational or auxiliary medicinal products ~~delivered directly to the subject ('direct delivery to subject')~~ shall be provided, including aspects of privacy protection and confidentiality. Information shall be included on ensuring that the product reaches the intended recipient (e.g., the participant or their designee), ~~and~~ on maintaining the integrity and quality of the medicinal product (e.g., blinding, storage) throughout the supply chain, **and on ensuring clinical trial validity.**

- (ap) a justification for description of the any proposed use of electronic informed consent. If electronic means are used, the sponsor shall ensure that the systems used have proportionate security levels, and that safeguards regarding confidentiality are in place. ~~inclusion of subjects that can only provide an informed consent through electronic means shall be provided.~~
- (aq) if the sponsor used an AI tool or system, a clear explanation of the specific purpose of the use of that tool and a description of the processes in which it is used. If an AI tool is certified according to Regulation (EU) 2024/1689 laying down harmonised rules on artificial intelligence, the sponsor shall provide the information contained in the certificate. In both cases, the information may be submitted in supporting documents under the condition that they are listed in and submitted together with the protocol.

G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

36bis Where applicable, in the case of advanced therapy investigational medicinal products, a declaration of the sponsor, in accordance with Article 4a(2) of Regulation (EC) No 1394/2007.

• **Table 1: Content of the simplified IMPD**

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The investigational medicinal product is authorised or has a marketing authorisation in an ICH country and is used in the clinical trial:			
— within the conditions of the SmPC	SmPC		
— outside the conditions of the SmPC	SmPC	If appropriate	If appropriate
— after modification (for example blinding)	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the investigational medicinal product is authorised or has a marketing authorisation in an ICH country and the investigational medicinal product is supplied by the marketing authorisation holder	SmPC+P+A	Yes	Yes
The investigational medicinal product is not authorised and has no marketing authorisation in an ICH country but the active substance is contained in an authorised medicinal product, and			
— is supplied by the same manufacturer	SmPC+P+A	Yes	Yes
— is supplied by another manufacturer	SmPC+S+P+A	Yes	Yes
The investigational medicinal product was subject to a previous clinical trial application and authorised in at least 2 Member States and has not been modified, and			
— no new data are available since last amendment to the clinical trial application,	Reference to previous submission		
— new data are available since last amendment to the clinical trial application,	New data	New data	New data
— is used under different conditions	If appropriate	If appropriate	If appropriate

(S: Data relating to the active substance; P: Data relating to the investigational medicinal product; A: Additional information on Facilities and Equipment, Adventitious Agents Safety Evaluation, Novel Excipients, and Solvents for Reconstitution and Diluents)

Possibility to refer to an active substance master file, an additional quality master file, a certified platform technology master file or a corresponding active substance master file certificate granted by the Agency, or a certificate confirming that the quality of the substance is suitably controlled by the relevant monograph of the European Pharmacopeia

53a Where applicable, the sponsor may, instead of submitting all the relevant information on the quality of the active substance or any other substance present or used in the manufacture of the investigational medicinal product, include in the IMPD quality section an active substance master file (ASMF), or any other additional quality master file or a corresponding valid **active substance master file certificate granted by the Agency,** or a certificate **of suitability which confirms that** confirming that the quality of the substance **concerned** is suitably controlled by the relevant monograph of the European Pharmacopeia, or where relevant a certified platform technology master file as referred to in [revised Directive 2001/83/EC] provided that the active substance is produced in accordance with the master file or its certificate. **Where such a reference is made, the corresponding certificate shall have been already granted, or the ASMF or other referenced master file must have already been evaluated with a positive outcome, prior to the submission of the clinical trial application.** Such reference shall be accompanied by a letter of access from the substance manufacturer when the substance is not manufactured by the sponsor. The manufacturer or certificate holder shall, however, provide the sponsor with all of the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the sponsor that it shall ensure batch to batch consistency. The holders of the master files or related certificates shall not modify the details of the master file without informing the sponsor. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities and sponsor, as applicable. **When using this possibility,** ~~the~~ the sponsor shall include ~~in the simplified IMPD~~ any relevant data to the active substance or its manufacturing which is not covered in the referenced master file or certificate. In addition, all quality data relating to the investigational medicinal product and its manufacturing together with the non-clinical and clinical data shall be provided.

Ga - INVESTIGATIONAL MEDICINAL PRODUCT CORE DOSSIER (IMP-CD)

54a. The IMP-CD as a tool to support the development of **use of the an** investigational medicinal product **in multiple clinical trial applications** shall ~~gather~~ **include** information relevant to regulatory processes. The IMP-CD shall describe the scope of authorised use in clinical trials, including the intended population(s), route(s) and mode(s) of administration, dosage range(s), exposure range, development stage(s), **therapeutic indications(s)**, and as appropriate, relevant parameters that determine its applicability to clinical trials.

The IMP-CD contains product specific data and information in the IB and IMPD in agreement with Annex I points E and G. GMP-related documentation may be included in accordance with Annex I point F.

When using a reference to an approved IMP-CD in **the application for an intended corresponding** a clinical trial application, the sponsor shall confirm that the **use proposed in the** intended corresponding clinical trial falls within its defined scope **the scope of authorised use** as described in **the first subparagraph above** ~~point 1.~~

Complementary, clinical trial specific information may be provided in the application dossier of the corresponding clinical trial.

54b. ~~Possibility to refer to an active substance master file, an additional master file, a platform technology master file or a corresponding certificate, or a certificate confirming that the quality of the substance is suitably controlled by the relevant monograph of the European Pharmacopeia, or a certified platform technology master file as referred to in [REVISED Directive 2001/83/EC]. Where applicable, the sponsor may, instead of submitting all the relevant information on the quality of the active substance or any other substance present or used in the manufacture of the investigational medicinal product, include in the IMPD quality section an active substance master file (ASMF), or any other additional quality master file or a corresponding valid certificate, or a certificate confirming that the quality of the substance is suitably controlled by the relevant monograph of the European Pharmacopeia, or where relevant a certified platform technology master file as referred to in [revised Directive 2001/83/EC] provided that the active substance is produced in accordance with the master file or its certificate. Such reference shall be accompanied by a letter of access from the substance manufacturer when the substance is not manufactured by the sponsor. The manufacturer or certificate holder shall, however, provide the sponsor with all of the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the sponsor that it shall ensure batch to batch consistency. The holders of the master files or related certificates shall not modify the details of the master file without informing the sponsor. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities and sponsor, as applicable. The sponsor shall include in the simplified IMPD any relevant data to the active substance or its manufacturing which is not covered in the referenced master file or certificate. In addition, all quality data relating to the investigational medicinal product and its manufacturing together with the non-clinical and clinical data shall be provided.~~

I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

56. If available, a copy of the ~~summary~~ of scientific advice of the Agency, or of any Member State or third country, with regard to the clinical trial shall be submitted.

Part II

General principle:

Without prejudice to Article 26 and Article 69 concerning translations of part I documents, the application dossier for an application limited to Part II of the assessment report referred to in Article 11 and the application dossier for an application referred to in Article 14 shall be limited to sections K to S of this Annex.

L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)

61. All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent, or other alternative means according to Article 29(1) for recording informed consent. **If electronic means are used, the sponsor shall ensure that the systems used have proportionate security levels, and that safeguards regarding confidentiality are in place.**
62. A description of procedures relating to informed consent for all subjects, and in particular:
- (f) in case of using electronic informed consent, a description of the electronic system and the procedure to inform, obtain, document and store the informed consent.

M. SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)

65. Description of the qualification of the **principal** investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care shall be described.
66. Any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the **principal** investigators shall be presented.

S. ANY TRANSLATION OF DOCUMENTS FROM **PART I OF** ANNEX Ia REQUIRED IN THE NATIONAL LANGUAGE OF THE MEMBER STATE CONCERNED in accordance with Article 26 and Article 69.

This submission may include, depending on the requirements of the Member State concerned, but is not limited to, Cover Letter, Scientific synopsis, Lay summary, Labels and Patient-facing documents **related to primary and secondary trial endpoints** from Part I of the application dossier.’
