Council of the European Union

Brussels, 4 July 2014
(OR. en)

11423/14

LIMITE

PHARM 49
SAN 269
MI 509
COMPET 429
CODEC 1548

Interinstitutional Files:
2012/0266 (COD)
2012/0267 (COD)

NOTE

From:	General Secretariat of the Council
To:	Working Party on Pharmaceuticals and Medical Devices
No. prev. doc.:	10451/13 PHARM 30 SAN 200 MI 497 COMPET 400 CODEC 1320
No. Cion doc.:	14493/12 PHARM 71 SAN 215 MI 597 COMPET 600 CODEC 2305 14499/12 PHARM 72 SAN 216 MI 598 COMPET 599 CODEC 2312
Subject:	Proposal for a Regulation of the European Parliament and of the Council on **Medical devices**, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 Proposal for a Regulation of the European Parliament and of the Council on ***in vitro* diagnostic medical devices** - *Presidency proposal for Chapter VI of both proposals*

Delegations will find attached Presidency proposals for new texts for Chapters VI of both proposals. The text of Chapter VI of the Proposal for a Regulation on Medical devices is set out in Annex A and the text of Chapter VI of the Proposal for a Regulation on *in vitro* diagnostic medical devices is et out in Annex B.

The Presidency has also prepared one background text relating to each of the two annexes. These background texts are set out below.

Annex A contains, on pages 7, 10, 14, 16 and 22 boxes that are related to the Presidency questionnaire set out in document DS 1306/14.

Annex A (Medical devices)

In order to prepare the draft text of Chapter VI and related Annex XIII and XIV of the proposed Regulation on Medical devices, the following documents were examined:

1. The official documents sent by the Secretariat, to report positions by individual member states. These are:
   DS 1028/13, AT DS 1288/13 FR DS 1342/13, AT DS 1345/13, UK DS 1346/13, NL DS 1388/13 DS 1358/13 DK DS 1446/13, AT DS 1519/13, EN DS 1520/13 , FR DS 1572/13, EN DS 1773/13, SE DS 1002/14, DE. DS 1519/13 IT DS 1341/13 SE DS1411/13 LT DS 1572/13 IT. 16791/13 IE
2. The footnotes document prepared by the Secretariat, which reports the positions expressed verbally in the debate (DS 10451/13).
3. The document prepared by technical WG set up by the Irish Presidency on annex XII and XIV (Working Doc. MDEV-21 N ° 4) and 16791/13 IE "result of the collaboration of the Irish Presidency with the delegations' experts."
4. The Document prepared by the Chair of a technical meeting on Chapter VI held in Brussels at the Austrian embassy on 21st may 2014 "Final Report Technical Meeting on Clinical Investigations (DS 1286/14 AT).

The current proposal is based on acceptance, according to the following principles (in order of priority), of the proposals :

1. are clearly expressed and shared by several Member States;
2. are made by few/single Member State but who are in line with the framework.
3. in cases where there is doubt, the Italian Presidency intends to put a series of key questions and statements to which Member States should answer in writing (e.g. 'agree', 'disagree', 'neutral') on the main issues relevant to that chapter.

This will allow the Italian Presidency to propose a text which should represent the views of the majority of Member States and which should become the basis for the Council Position.

The present draft shows a possible text that will be modified on the basis of the answers given by the Members States in the questionnaire.

Text conventions in Annex A (Medical devices)

Additions to the Commission proposal are set out in **bold underline**.

Deletions of text in the Commission proposal are set out in ~~strikethrough~~.

Text in *italics* (apart from article numbers and headings) is original Commission text that the Presidency sees a specific need to discuss.

Annex B (*In vitro* diagnostic medical devices):

In order to prepare the draft text of Chapter VI and related Annex XII and XIII of the proposal on *In vitro* diagnostic medical devices the following documents were examined:

1. The footnotes document prepared by the Secretariat, which reports the positions expressed verbally in the debate (DS 10451/13).
2. The official documents sent by the Secretariat, to report positions by individual Member States. These are:
   DS 1445/13, AT - DS 1468/13, AT - DS 1773/13, SE.
3. The document prepared by the Irish Presidency with the delegations' experts on Annex XII and XIII (ST 17945/13).

Footnotes in Annex B reflect

(a) suggestions and comments included in the above mentioned documents or made at the meeting of the Working Party on 31 May 2013,

(b) comparisons with the text for Chapter VI of the Medical device proposal prepared by the Italian Presidency (set out in Annex A)

Text conventions in Annex B (*In vitro* diagnostic medical devices)

Additions to the Commission proposal are set out in **bold underline**.

Deletions of text in the Commission proposal are set out in ~~strikethrough~~.

Suggested additions by comparison with Proposal on Medical Devices are indicated by […].

Suggested deletions by comparison with Proposal on Medical Devices are indicated as highlighted text.

The present draft shows a possible text that will be modified on the basis of the answers given by the Members States in the questionnaire referred to the Proposal on Medical Devices

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009

(Text with EEA relevance)

Chapter VI

Clinical evaluation and clinical investigations

Article 49

Clinical evaluation

1. **Confirmation of conformity with the requirements concerning the characteristics and performances referred to in Section 1 of Annex I under the normal conditions of use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit/risk ratio referred to in Sections 1 and 5 of Annex I, shall be based on clinical data providing sufficient clinical evidence.**[1] [2]

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate compliance with the relevant essential requirements on safety and performance which shall correspond to the characteristics of the device and its intended purpose.[3]

---

1 **DS 1773/13 SE - DS 1002/14 DE - 16791/13** Irish Presidency **MDEV-21** Page 3

2 First sentence is moved from Annex XIII.

3 **10451/13 UK**: Replace this paragraph in accordance with DS 1345/13, **DE, FR, ES, PT**: Support. Cion: Agreed with this approach. **SE:** Add "*to support the assessment of conformity of the device*". **DS 1345/13 UK - DS 1002/14 DE -DS 1342/13 AT- DS 1773/13 SE . 16791/13** Irish Presidency MDEV-21 Irish Presidency Report of the Meeting of Experts on 21 and 22 May 2013

~~Manufacturers~~ **To that end, manufacturers** shall **plan,** conduct **and document a** clinical evaluation in accordance with ~~the principles set out in~~ this Article and Part A of Annex XIII.[4]

2. A clinical evaluation shall follow a defined and methodologically sound procedure based on ~~either of~~ the following:

(a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose **and use**[5] of the device, where the following conditions are satisfied:

- it is demonstrated that the device **and its use**[6] subject to clinical evaluation and the device to which the data relate are equivalent[6],
- the data adequately demonstrate compliance with the relevant general safety and performance requirements **in respect to technical, biological and clinical characteristics**, **including usability in the intended context of use**[7];

(b) a critical evaluation of the results of all clinical investigations**, with preference to those**[8] performed in accordance with Articles 50 to 60 and Annex XIV;

(c) a critical evaluation of the combined clinical data referred to in points (a) and (b).

(d) a comparison between the device and other treatments employed in the current clinical practice, if any.[9]

---

4 **10451/13 AT** Replace this paragraph with "*Manufacturers shall plan, conduct and document the clinical evaluation in accordance with this Article and Part A of Annex XIII."* **IT, PT**: Support.**DS 1342/13 AT**

5 **10451/13 AT foot notes 9/10/11/13, PT, IT support -DS 1342/13 AT -DS-1519/13 IT**

6 **10451/13 DE**: 'Equivalent' should be defined. **FR**: Support. **16791/13** Irish Presidency (foot note 5)

7 **DS 1002/14 DE**

8 **10451/13 AT**: Add "*, with preference to those*" **IT, PT**: Support. **DS** 1342/13 **AT**

9 **DS 1002/14 DE DS-1519/13 IT**

2a. In the case of implantable devices and devices falling within class III, the clinical evaluation shall include the assessment of a clinical investigation performed with the device concerned. In case of a modification of an existing implantable device or an existing device falling within class III, another validation methodology is also appropriate, if it gives sufficient evidence.[10]

3. Where demonstration of conformity with general safety and performance requirements based on clinical ~~data~~ **evidence** is not deemed appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performances intended and the claims of the manufacturer. The adequacy of demonstration of conformity with the general safety and performance requirements based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and pre-clinical evaluation, has to be duly substantiated in the technical documentation referred to in Annex II.

4. The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from the implementation of the manufacturer's post-market surveillance plan referred to in Article 8(6). **For devices classified as class III and implantable devices, the summary of safety and clinical performance referred to in Article 26(1) shall be updated at least annually with these data.**[11]

5. The clinical evaluation**, its results** and ~~its outcome~~ **the clinical evidence derived from it**[12] shall be documented in a clinical evaluation report referred to in Section 6 of Part A of Annex XIII which shall be ~~included or fully referenced in~~ **part of**[13] the technical documentation referred to in Annex II relating to the device concerned.

---

[10] **DS 1002/14 DE - DS 1388/13 FR "***Given the importance of this requirement, it should appear in the text of the Regulation, in Article 49 (Clinical evaluation) and not in one of the Annexes. This principle should be clearly set out in Article 49, between paragraphs 2 and 3."* **- DS 1346/13NL - MDEV-21 IE**

[11] **10451/13 UK: Add "***For devices classified as class III and implantable devices, the summary of safety and clinical performance referred to in Article 26(1) shall be updated at least annually with these data.***" FR, ES, HU, PT: Support - DS 1345/13UK - DS -1519/13 IT**

[12] **DS 1002/14 DE**

Article 50

General requirements regarding clinical investigations

1. Clinical investigations shall be subject to Articles 50-60 and Annex XIV if they are conducted for one or more of the following purposes:

   (a) to verify that, under normal conditions of use, devices are designed, manufactured and packaged in such a way that they are suitable for one or more of the specific purposes of a medical device referred to in number (1) of Article 2(1), and achieve the performances intended as specified by the manufacturer;

   (b) to verify that devices achieve the intended benefits to the patient as specified by the manufacturer;

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

Box 1

QUESTIONNARIE[13] Clinical investigations not planned for CE marking and commercial purposes

E.g. possible text

In order to protect health, safety and well being of subjects, the clinical investigations of medical devices planned for non commercial purposes shall be carried out in accordance with scientific and ethical principles set out in this chapter and Annex XIII and XIV.

Any requirement by CA for notification or authorization/tacit approval for such investigations is at discretion of Member States. No Member State shall have to lower its current standards.

[13] **Questionnaire** / **10451/13 21 PT**: Chapter should also apply to studies that are not for regulatory purposes **AT:** Provision could be extended to cover all investigations of medical devices**. BE, FR, HU, PT, SI, SK: Support** /. Cion: Could consider this extension of the scope. **DS 1342/13 AT / DS-1519/13 IT DS 1286/14 AT:CIE Final report Technical Meeting on Clinical investigation**

2. Where the sponsor is not established in the Union, he shall ensure that a ~~contact person~~[14] **legal representative** is established in the Union. **The legal representative has to take the legal responsibility that the clinical investigation is conducted according to the provisions of this Regulation.** ~~That contact person~~ **The legal representative** shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to ~~that contact person~~ **the legal representative** shall be considered as communication to the sponsor.

3. Clinical investigations shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected and that the clinical data generated in the clinical investigation are going to be reliable and robust.

~~4. Clinical investigations shall be designed, conducted, recorded and reported in accordance with the provisions of Articles 50 to 60 and of Annex XIV.~~

5. A clinical investigation according to paragraph 1 may be conducted only where all of the following conditions are met:[15]

(a) the clinical investigation was subject to an authorisation by a competent authority of the Member State(s) concerned, in accordance with this Regulation, unless otherwise stated,

(b) an independent Ethics Committee, set up according to national law, has issued a favourable opinion on the planned clinical investigation.

(c) the sponsor or its legal representative is established in the Union.

(d) the foreseeable risks and inconveniences to the subject are medically justifiable weighed against the medical device's potential relevance for medicine;

(e) the subject or, where the subject is not able to give informed consent, his or her legal representative has given informed consent,

---

[14] **10451/13 AT:** Not sufficient with regard to liability issues in case of harm to European patients. **DE, FR, HU, NL, PL, PT, SE: Support / DS 1446/13 AT / DS-1519/13 IT**

[15] **DS 1002/14 DE** proposes the elimination of p. 3 and 4 and proposes the articles 3 and 4 modified.

(f) **the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, who is a physician or in the case of a dental investigational device, a dentist, to understand the objectives, risks and inconveniences of the clinical investigation, and the conditions under which it is to be conducted and has also been informed about the purpose and scope of the acquisition and use of personal data, and about the right to withdraw from the clinical investigation at any time without any resulting detriment as well as the possible medical consequences of the withdraw;**

(g) **the subject has not been committed to an institution by virtue of an order issued either by the courts or by an authority**

(h) **the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded,**

(i) **in the event that a person is killed or a person's body or health is harmed or impaired in the course of the clinical investigation, an insurance policy according to Article XX, which also provides compensation when no one else accepts liability for the damage exists,**

(j) **where appropriate, biological safety testing and pre-clinical evaluation reflecting the latest scientific knowledge or any other test deemed necessary in the light of the medical device's intended purpose has been conducted,**

(k) **the technical safety of the medical device with regard to its use has been proven, taking into consideration the state of the art as well as provisions in the field of occupational safety and accident prevention,**

6. **Any subject may, without any resulting detriment, withdraw from the clinical investigation at anytime by revoking his or her informed consent. The withdrawal of the consent shall not affect the activities carried out based on consent before its withdrawal.**

Box 2

QUESTIONNARE Article 50 Protection of subjects involved in clinical investigations

Art 50 and Annex XIV provide principles for protection of subjects involved in CI.

Items excluded from the present proposal of Regulation are: insurance/damage compensation, suitability of investigators and clinical sites, informed consent, clinical investigations on incapacitated subjects, on minors, clinical investigations in emergency situations.

Do the delegations agree that above items are captured in the Regulation?
Do the delegations agree that basic general principles connected to above items should be fixed in the Regulation?
Do the delegations prefer that above items are regulated exclusively by national provision ?

Article 51

Application for clinical investigations

~~1. Before making the first application, the sponsor shall procure from the electronic system referred to in Article 53 a single identification number for a clinical investigation conducted in one site or multiple sites, in one or more than one Member State. The sponsor shall use this single identification number when registering the clinical investigation in accordance with Article 52.~~

2. The sponsor of a clinical investigation shall submit **by means of the electronic system referred to in Article 53** an application to the Member State(s) in which the investigation is to be conducted accompanied by the documentation referred to in Chapter II of Annex XIV. **The electronic system referred to in Article 53 shall generate a union wide unique single identification number for this clinical investigation which shall be used for all relevant communication in relation to the clinical investigation concerned.**[16] Within ~~six~~ **ten**[17] days after receipt of the application, the Member State concerned shall notify the sponsor whether the clinical investigation falls within the scope of this Regulation and whether the application is complete.

~~Where the Member State has not notified the sponsor within the time period referred to in the first subparagraph, the clinical investigation shall be considered as falling within the scope of this Regulation and the application shall be considered complete.~~[18]

---

[16] **DS 1002/14 DE DS 1446/13 AT - QUESTIONNARIE IT- INFRASTRUCTURE**

[17] **DS 1002/14 DE – DS 1046/13 AT- 10451/13: AT, CY, DK, EE, ES, FR, IT, NL, PL, PT, SE:** Timeline is too short. **CZ, LV, SE**: Are these calendar or working days? Cion**:** Calendar days. **DE**: Replace "*six days*" by "*ten days*". **SK:** Support **SI**: Replace "*six days*" by "*15 days*". **FR**: Replace "*six days*" by "*18 days* /. **DS 1002/14 DE / 10451/13 DK, EE, ES, FR, IT, NL, PL, PT, SE**: Timeline is too short. DE: Replace "*six days*" by "*30 days*". FR: Replace "*six days*" by "5 *days* **AT, CY, DK, EE, ES, FR, IT, LV, NL, PL, PT, SE:** Timeline is too short**. AT: Replace "**35 days" by "60 days**". ES, HU, PT, SE, SI, SK, UK: Support.**

[18] **10451/13: SI**: Scrutiny reserve on tacit approval **DS 1002/14 DE** no tacit assumption of completeness of the application nor a tacit decision that the investigation is falling within the scope of the Regulation

3. Where the Member State finds that the clinical investigation applied for does not fall within the scope of this Regulation or that the application is not complete, it shall inform the sponsor thereof and shall set a maximum of six **30**[18] days for the sponsor to comment or to complete the application.

Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as ~~withdrawn~~ **rejected**.

~~Where~~ ~~t~~**T**he Member State has ~~not~~ **to** notif**y**~~ied~~ the sponsor ~~according to paragraph 2~~ within ~~three~~ **ten**[18] days following receipt of the comments or of the completed application~~,~~ **whether** the clinical investigation ~~shall be~~ **is** considered as falling within the scope of this Regulation and the application ~~shall be considered~~ **is** complete**d**.[19]

4. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 **or 3** shall be the validation date of the application. ~~Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 3.~~[19]

4a. In the period during which the application is being examined the Member State may request, on a single occasion, additional information from the sponsor. The expiry of the deadline pursuant paragraph 5 b) (second indent) shall be suspended from the date of the request until such time as the additional information has been received.[19]

[19] **DS 1002/14 DE -DS 1519/13 IT**

5. The sponsor may start the clinical investigation in the following circumstances:[20]

(a) in the case of investigational devices classified as class **I** ~~III and implantable or long-term~~ **or in the case of non-**invasive devices classified as class IIa ~~or IIb, as soon as the Member State concerned has notified the sponsor of its approval~~ **immediately after the validated date of application described in paragraph 4, provided that the competent Ethics committee in the Member State concerned has issued a favourable opinion**;

(b) in the case of investigational devices other than those referred to in point (a)**:**

- **as soon as the Member State concerned has notified the sponsor of its approval and the competent Ethics committee in the Member State concerned has issued a favourable opinion, or**
- **after the expiry of 60 days after the validation date referred to in paragraph 3, unless the Member State concerned has notified the sponsor within that period of its refusal and provided that the Ethics committee in the Member State concerned has issued a favourable opinion**[21]

~~immediately after the date of application provided that the Member State concerned has so decided and that evidence is provided that the rights, safety and well-being of the subjects to the clinical investigation are protected;~~

~~(c) after the expiry of 35 days~~[21] ~~after the validation date referred to in paragraph 4, unless the Member State concerned has notified the sponsor within that period of its refusal based on considerations of public health, patient safety or public policy~~.

---

[20] **10451/13 DK**: Time should be afforded to allow Member States to consult Ethics Committees. **AT, DE**: Support. **DK**: A deadline should be used in this provision. Cion: Express authorisation envisaged. **AT**: Replace "*date of application*" by "*date of validation*". **DE**: Support.
AT, CY, DK, EE, ES, FR, IT, LV, NL, PL, PT, SE: Timeline is too short**. AT: Replace "**35 days" by "60 days**". ES, HU, PT, SE, SI, SK, UK: Support.**

[21] **DS 1002/14 DE – DS 1446/13 AT**

Box 3

QUESTIONNARE

Article 51 Provisions concerning aspects of the CI

DS 1002/14 DE suggests that paragraphs 6 and 7 be deleted and are replaced by the following articles:

Article 51a: Assessment by Member States
Article 51b: Ethics Committee
Article 51c: Assessment by the Ethics Committee
Article 51d: Withdrawal, revocation and suspension of the authorisation or of the favourable opinion

Do the delegations agree that above items are captured in the Regulation?
Do the delegations agree that basic general principles connected to above items should be fixed in the Regulation?
Do the delegations prefer that above items are regulated exclusively by national provision?

6. *Member States shall ensure that the persons assessing the application do not have conflicts of interest and that they are independent of the sponsor, the institution of the investigation site(s) and the investigators involved, as well as free of any other undue influence.*

Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. In the assessment, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account.[22]

7. *The Commission shall be empowered to adopt delegated acts*[22] *in accordance with Article 89 amending or supplementing, in the light of technical progress and global regulatory developments, the requirements for the documentation to be submitted with the application for the clinical investigation that is laid down in Chapter II of Annex XIV.*[23]

Article 52

~~*Registration of*~~ ***Public access to information on*** *clinical investigations*[25]

1. ~~Before commencing the clinical investigation, the sponsor shall enter in~~ **The following information regarding the clinical investigation shall be accessible to the public through** the electronic system referred to in Article 53[16] [24] ~~the following information regarding the clinical investigation~~:
   (a) the single identification number of the clinical investigation;
   (b) the name and contact details of the sponsor and, if applicable, his ~~contact person~~ **legal representative** established in the Union;
   (c) the name and contact details of the natural or legal person responsible for the manufacture of the investigational device, if different from the sponsor;
   (d) the description of the investigational device;
   (e) the description of the comparator(s), if applicable;
   (f) the purpose of the clinical investigation;
   (g) the status of the clinical investigation.

2. Within one week of any change occurring in relation to the information referred to in paragraph 1, the sponsor shall update the relevant data in the electronic system referred to in Article 53.

---

22 **10451/13 : AT, CY, DK, ES, SE**: Reserve on delegated acts

23 **DS 1002/14 DE proposes the elimination of p. 6 and** 7: *Rationale: Partially moved to Article 51a, the involvement of non-scientists and patients is covered by the proposed articles (51 a, b, c, d.*

24 **DS 1002/14 DE-DS 1446/13 AT**

3. The information **referred to in paragraph 1** shall be accessible to the public, ~~through the electronic system referred to in Article 53,~~ unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:
   (a) protection of personal data in accordance with Regulation (EC) No 45/2001;
   (b) protection of commercially sensitive information;
   (c) effective supervision of the conduct of the clinical investigation by the Member State(s) concerned.

4. No personal data of subjects participating in clinical investigations shall be publicly available.

Article 53

Electronic system on clinical investigations

Box 4

QUESTIONNARE

IT Infrastructure

Article 53 (Electronic system on clinical investigations) provides that the Commission shall set up and manage an electronic system to collect and process the information related to clinical investigations conducted **in more than one Member State** in case of a single application in accordance with Article 58 and related SAE reporting.

Since clear picture and budgetary outlook is necessary on this matter,

1. Do the delegations agree to capture also national clinical investigations and related SAE reporting in the above mentioned electronic system?

In the present proposal of Regulation, the electronic information exchange on CI start, amendment, temporary alt/suspension, end is currently lacking. It would be important to provide the MS with the electronic tool for managing post-authorization information (see DS 1286/14)**.**

2. Do the Delegations agree to include also the information concerning the above mentioned issues in the electronic system?

1. The Commission shall, in collaboration with the Member States, set up**,** ~~and~~ manage **and maintain** an electronic system to create the single identification numbers for clinical investigations **and to be used as an entry point for the submission of application** referred to in Article 51(1) and **for all other submission of data, for the exchange of information relating to clinical investigations in accordance with this Regulation between the Member States and between them and the Commission, and for reporting on serious adverse events and device deficiencies referred to in Article 59.**[16] ~~to collate and process the following~~ information :

   ~~(a) the registration of clinical investigations in accordance with Article 52;~~

   ~~(b) the exchange of information between the Member States and between them and the Commission in accordance with Article 56;~~

   ~~(c) the information related to clinical investigations conducted in more than one Member State in case of a single application in accordance with Article 58;~~

   ~~(d) reports on serious adverse events and device deficiencies referred to in Article 59(2) in case of a single application in accordance with Article 58.~~

2. When setting up the electronic system referred in paragraph 1, the Commission shall ensure that it is interoperable with the EU database for clinical trials on medicinal products for human use set up in accordance with Article […] of Regulation (EU) No […/…]. With the exception of the information referred to in Article 52, the information collated and processed in the electronic system shall be accessible only to the Member States and to the Commission.

3. The Commission shall be empowered to adopt delegated acts in accordance with Article 89 determining which other information regarding clinical investigations collated and processed in the electronic system shall be publicly accessible to allow interoperability with the EU database for clinical trials on medicinal products for human use set up by Regulation (EU) No […/…]. Article 52(3) and (4) shall apply.

Article 54

Clinical investigations with devices authorised to bear the CE marking

1. Where a clinical investigation is to be conducted to further assess a device which is authorised in accordance with Article 42 to bear the CE marking and within its intended purpose referred to in the relevant conformity assessment procedure, hereinafter referred to as 'post-market clinical follow-up investigation', the sponsor shall notify the Member States concerned at least 30 days prior to their commencement if the investigation would submit subjects to additionally invasive or burdensome procedures. **The notification shall be made by means of the electronic system referred to in Article 53. It shall be accompanied by the documentation referred to in Chapter II of Annex XIV. Article 50 paragraph 5 points (b) to (i)**[16] ~~Article 50(1) to (3)~~, Article 52, Article 55, Article 56(1), Article 57(1), the first subparagraph of Article 57(2) and the relevant provisions of Annex XIV shall apply.

2. If the aim of the clinical investigation regarding a device which is authorised in accordance with Article 42 to bear the CE marking is to assess such device for a purpose other than that referred to in the information supplied by the manufacturer in accordance with Section 19 of Annex I and in the relevant conformity assessment procedure, Articles 50 to 60 shall apply.

Article 54a[23]

Modifications to a clinical investigation

The sponsor shall notify the Member State(s) concerned any changes made to the documents submitted pursuant to Article 51 paragraph 1 after having received an approval or favourable opinion pursuant Article 51 paragrah 5. The notification shall by made by means of the electronic system referred to in Article 53. The changed documents shall be attached to the notification and the changes shall be marked.[16]

Article 55

Substantial modifications to a clinical investigation

~~1.~~ If the sponsor ~~introduces~~ **intends to introduce** modifications to a clinical investigation that are likely to have a substantial impact on the safety or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation, he shall notify **by means of the electronic system referred to in Article 53**[16] the Member State(s) concerned **and the Ethics committee concerned** of the reasons for and the content of those modifications. The notification shall be accompanied by an updated version of the relevant documentation referred to in Chapter II of Annex XIV**, changes shall be marked**. ~~2.~~ The sponsor may implement the modifications referred to in paragraph 1 at the earliest 30 days after notification, unless the Member State concerned has notified the sponsor of its refusal based on considerations of public health, patient safety or public policy.

Article 56

Information exchange between Member States

1. Where a Member State has refused, suspended or terminated a clinical investigation, or has called for a substantial modification or temporary halt of a clinical investigation, or has been notified by the sponsor of the early termination of a clinical investigation on safety grounds, that Member State shall communicate its decision and the grounds therefor to all Member States and the Commission by means of the electronic system referred to in Article 53.

2. Where an application is withdrawn by the sponsor prior to a decision by a Member State, that Member State shall inform all the other Member States and the Commission of that fact, by means of the electronic system referred to in Article 53.

Article 57

Information by the sponsor in the event of temporary halt or termination of a clinical investigation

1. If the sponsor has temporarily halted a clinical investigation on safety grounds **or has early terminated a clinical investigation**, he shall inform the Member States concerned within 15 days of the temporary halt **or early termination, providing a justification**.[23]

2. The sponsor shall notify each Member State concerned of the end of a clinical investigation in relation to that Member State~~, providing a justification in the event of early termination~~. That notification shall be made within 15 days from the end of the clinical investigation in relation to that Member State.

2a. If the investigation is conducted in more than one Member State the sponsor shall notify all Member States concerned of the overall end of the clinical investigation. That notification shall be made within 15 days from the overall end of the clinical investigation.

3. Within one year from the end **or early termination**[23]of the clinical investigation, the sponsor shall submit to the Member States concerned ~~a summary of the results of the clinical investigation in form of~~ a clinical investigation report referred to in Section 2.7 of Chapter I of Annex XIV. Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year, it shall be submitted as soon as it is available. In this case, the clinical investigation plan referred to in Section 3 of Chapter II of Annex XIV shall specify when the results of the clinical investigation are going to be submitted, together with an explanation.

Article 58

Clinical investigations conducted in more than one Member State[25] [26] [27]

[25] **DS 1286/14** Final Report Technical Meeting on Clinical Investigations; 21.5.2014
Coordinated assessment procedure :Necessary element: **define assessment process and content in more detail** to assure homogeneous and mutually reliable procedure!
2 options:
(a) Start with mandatory Coordinated Procedure, but stretching gradually its content over time:
UK presented the proposal shown in this document on CAP procedures.
(b) Start with voluntary CAP for a certain time > collect experience
FR is working on the development of a further proposal

[26] **DS 1014/14, DE proposes the elimination of article 58**: «In our view a mandatory coordinated approval procedure in the case of clinical investigations in more than one Member State should not yet be part of the Regulation. We think Member States have not gained sufficient experience on coordinating approval of clinical investigations. On the basis of the proposed and more detailed legal provisions on clinical investigation and the approval procedure Member States should gain practical experience first and coordinate their assessments voluntarily. This could be the basis for a future mandatory coordination mechanism. »

[27] Questionnaire

Box 5

QUESTIONNARE

Article 58 Coordinated Assessment Procedure

1) Start with mandatory Coordinated Assessment Procedure (CAP), but stretching gradually its content over time

UK presented the suggestion shown in document DS 1286/14 on CAP procedures

2) Start with voluntary CAP for a certain time, collect experience, then report by the Commission on its functioning and, after positive experience, delegated/implementing act of the Commission on mandatory CAP, maybe with appropriate modifications**;**

FR is working on the development of a further proposal (DS 1286/14)

Does your delegation agree with the establishment of this proposed Coordinated Assessment Procedure?

If YES, does your Delegation prefer that each Member State might decide whether to participate in the Coordinated Assessment Procedure (voluntary basis by the MSs)?

If YES, does your Delegation agree that this new coordinated assessment approach might be developed into two phases: 1st phase on a voluntary basis for both sponsor and MS; 2nd phase, on a mandatory basis with a delegated act of the Commission, after collecting/reporting positive experience?

Or As an alternative does your Delegation prefer to start with a mandatory Coordinated procedure (mandatory for MS), but stretching gradually its content (joint validation>joint assessment>joint decision) over time in order to be progressive in this kind of cooperation?

With reference to the question above, according to the above mentioned article, the sponsor **may** submit a single application in case of multinational clinical investigations. Therefore, sponsor seems to be in the position of choosing whether to submit a single application for all the MSs concerned or whether to submit as many applications as the number of the MSs concerned is, as it is the current procedure.

Does your Delegation support the possibility of the sponsor of choosing the assessment for multinational clinical investigations (voluntary for Sponsor)?

As an alternative does your Delegation prefer a mandatory Coordinated Assessment Procedure (the sponsor [...] **shall submit** a single application [...])

1. By means of the electronic system referred to in Article 53, the sponsor of a clinical investigation to be conducted in more than one Member State may submit, for the purpose of Article 51, a single application that, upon receipt, is transmitted electronically to the Member States concerned.

2. In the single application, the sponsor shall propose one of the Member States concerned as coordinating Member State. If that Member State does not wish to be the coordinating Member State, it shall agree, within six days of submission of the single application, with another Member State concerned that the latter shall be the coordinating Member State. If no other Member State accepts to be the coordinating Member State, the Member State proposed by the sponsor shall be the coordinating Member State. If another Member State than the one proposed by the sponsor becomes coordinating Member State, the deadline referred to in Article 51(2) shall start on the day following the acceptance.

3. Under the direction of the coordinating Member State referred to in paragraph 2, the Member States concerned shall coordinate their assessment of the application, in particular of the documentation submitted in accordance with Chapter II of Annex XIV, except for Sections 3.1.3, 4.2, 4.3 and 4.4 thereof which shall be assessed separately by each Member State concerned.

   The coordinating Member State shall:

   (a) within 6 days of receipt of the single application notify the sponsor whether the clinical investigation falls within the scope of this Regulation and whether the application is complete, except for the documentation submitted in accordance with Sections 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV for which each Member State shall verify the completeness. Article 51(2) to (4) shall apply to the coordinating Member State in relation to the verification that the clinical investigation falls within the scope of this Regulation and that the application is complete, except for the documentation submitted in accordance with Sections 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV. Article 51(2) to (4) shall apply to each Member State in relation to the verification that the documentation submitted in accordance with Sections 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV is complete;

(b) establish the results of the coordinated assessment in a report to be taken into account by the other Member States concerned when deciding on the sponsor's application in accordance with Article 51(5).

4. The substantial modifications referred to in Article 55 shall be notified to the Member States concerned by means of the electronic system referred to in Article 53. Any assessment as to whether there are grounds for refusal as referred to in Article 55 shall be carried out under the direction of the coordinating Member State.

5, For the purpose of Article 57(3), the sponsor shall submit the clinical investigation report to the Member States concerned by means of the electronic system referred to in Article 53.

6. The Commission shall provide secretarial support to the coordinating Member State in the accomplishment of its tasks provided for in this Chapter.

Article 59

Recording and reporting of events occurring during clinical investigations

1. The sponsor shall fully record any of the following:
   (a) an adverse event identified in the clinical investigation plan as critical to the evaluation of the results of the clinical investigation in view of the purposes referred to in Article 50(1);
   (b) a serious adverse event;
   (c) a device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
   (d) new findings in relation to any event referred to in points (a) to (c).

2. The sponsor shall report to all Member States where a clinical investigation is conducted without delay any of the following **by means of the electronic system referred to in Article 53**:[16]

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

   (b) a device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

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

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

3. The sponsor shall also report to the Member States concerned any event referred to in paragraph 2 occurring in third countries in which a clinical investigation is performed under the same clinical investigation plan as the one applying to a clinical investigation covered by this Regulation.

4. In the case of a clinical investigation for which the sponsor has used the single application referred to in Article 58, the sponsor shall report any event as referred to in paragraph 2 by means of the electronic system referred to in Article 53. Upon receipt, this report shall be transmitted electronically to all Member States concerned.

   Under the direction of the coordinating Member State referred to in Article 58(2), the Member States shall coordinate their assessment of serious adverse events and device deficiencies to determine whether a clinical investigation needs to be terminated, suspended, temporarily halted or modified.

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

5. In the case of post-market clinical follow-up investigations referred to in Article 54(1), the provisions on vigilance contained in Articles 61 to 66 shall apply instead of this Article.

Article 60

Implementing acts

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

(a) harmonised forms for the application for clinical investigations and their assessment as referred to in Articles 51 and 58, taking into account specific categories or groups of devices;

(b) the functioning of the electronic system referred to in Article 53;

(c) harmonised forms for the notification of post-market clinical follow-up investigations as referred to in Article 54(1), and of substantial modifications as referred to in Article 55;

(d) the exchange of information between Member States as referred to in Article 56;

(e) harmonised forms for the reporting of serious adverse events and device deficiencies as referred to in Article 59;

(f) the timelines for the reporting of serious adverse events and device deficiencies, taking into account the severity of the event to be reported as referred to in Article 59.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(3).

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on *in vitro* diagnostic medical devices

(Text with EEA relevance)

Chapter VI
Clinical evidence[1]

Article 47

General requirements regarding clinical evidence

1. The demonstration of conformity with the general safety and performance requirements set out in Annex I, under normal conditions of use, shall be based on clinical evidence.

2. The clinical evidence shall support the intended purpose of the device as stated by the manufacturer **and be based on a continuous process of clinical evaluation, following a clinical evaluation plan**.

3. The clinical evidence shall ~~include~~ **provide scientifically valid assurance, including**[2] all the information supporting the scientific validity of the analyte, the analytical performance and, where applicable, the clinical performance of the device, as described in Section 1 of Part A of Annex XII **that the relevant general safety and performance requirements set out in Annex I, under normal conditions of use, are fulfilled**[3].

---

1 DE: Replace "*clinical evidence*" by "*clinical evaluation*" in line with Medical Devices Regulation.

2 AT: Replace "*include*" by "*provide scientifically valid assurance, including*" (DS 1468/13) HU, NL, PT: Support.

3 AT: Add "*, that the relevant general safety and performance requirements set out in Annex I, under normal conditions of use, are fulfilled.*" (DS 1468/13) HU, NL, PT: Support.

4. Where demonstration of conformity with the general safety and performance requirements based on clinical performance data or parts thereof is not ~~deemed appropriate~~ **applicable** [4], adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the characteristics of the device and, in particular, its intended purpose(s), the intended performance and the claims of the manufacturer. The adequacy of demonstration of conformity with the general safety and performance requirements based on the results of analytical performance evaluation alone shall be duly substantiated in the technical documentation referred to in Annex II.

5. The scientific validity data, the analytical performance data and, where applicable, the clinical performance data shall be summarised **in reports**[5] as part of a clinical evidence report[6] referred to in Section 3 of Part A of Annex XII. The clinical evidence report shall be included or fully referenced in the technical documentation referred to in Annex II relating to the device concerned.

6. The clinical evidence and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from implementation of the manufacturer's **post-market follow-up plan, as part of the**[7] post-market surveillance plan referred to in Article 8(6).

7. The manufacturer shall ensure that the device for performance evaluation complies with the general requirements of this Regulation apart from the aspects covered by the performance evaluation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the patient, user and other persons.

---

4 AT: Replace "*deemed appropriate*" by "*applicable*" (DS 1468/13) HU, NL, PT: Support.
5 AT: Add "*in reports*" (DS 1468/13) BE, HU, NL, PT: Support.
6 SE: Add a requirement that this report should be accessible to the general public. PT: Support.
7 AT: Add "*post-market follow-up plan, as part of the*" (DS 1468/13) HU, NL, PT: Support.

The manufacturer shall undertake to keep available to the competent authorities and the EU reference laboratories[8] the documentation allowing an understanding of the design, manufacture and performances of the device, including its expected performance, so as to allow assessment of conformity with the requirements of this Regulation. This documentation shall be kept for at least five years after the performance evaluation of the device in question has ended.

Article 48

General requirements regarding clinical performance studies

1. Clinical performance studies shall be subject to this Regulation if they are conducted for one or more of the following purposes:
   (a) to verify that, under normal conditions of use, the devices are designed, manufactured and packaged in such a way that they are suitable for one or more of the specific purposes of an in vitro diagnostic medical device referred to in number (2) of Article 2, and achieve the performance intended as specified by the manufacturers;
   (b) to verify that devices achieve the intended benefits to the patient as specified by the manufacturer;
   (c) to determine any limits to the performance of the devices, under normal conditions of use.[9]

2. Clinical performance studies shall be performed in circumstances similar to the normal conditions of use of the device.

[8] ES: Clarification on the role of EU reference laboratories in this context. PL: Support. Cion: EU reference laboratories are not involved in the procedures but must be informed so they can lay down guidelines.

[9] AT: Reserve on points (a)-(c). (DS 1445/13) - NL: What is the relationship between points (a) and (b)? DE: Support.

3. Where the sponsor is not established in the Union, he shall ensure that a contact person[10] [11] [12] […] is established in the Union. [13] […] That contact person[11] […] shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that contact person[11] shall be considered as communication to the sponsor.

4. All clinical performance studies **must be carried out in accordance with the Helsinki Declaration,**[14] shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in such clinical performance studies are protected and that the clinical data generated in the clinical performance study are going to be reliable and robust.

5. All clinical performance studies shall be designed, conducted, recorded and reported in accordance with Section 2 of Annex XII.

6. For interventional clinical performance studies, as defined in number (37) of Article 2, and for other clinical performance studies, where the conduct of the study, including specimen collection, involves invasive procedures or other risks for the subjects of the studies, the requirements set out in Articles 49 to 58 and in Annex XIII shall apply, in addition to the obligations laid down in this Article. **The same requirements shall apply by analogy to analytical performance studies of companion diagnostics.**[15]

---

10 AT: Not sufficient with regard to liability issues in case of harm to European patients. (DS 1445/13) DE, FR, HU, NL, PL, PT, SE: Support.

11 SK: Role and responsibilities of the contact person must be specified.

12 **MD Proposal** : replace "*contact person*"- by "*legal representative*"

13 **MD Proposal** : add "*The legal representative has to take the legal responsibility that the clinical [investigation] is conducted according to the provisions of this Regulation.* "

14 SE: Add "*must be carried out in accordance with the Helsinki Declaration"* (DS 1773/13)

15 AT: Add "*The same requirements shall apply by analogy to analytical performance studies of companion diagnostics*" (DS 1445/13)

Article 49

Application for interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies

1. Before making the first application, the sponsor shall procure from the electronic system referred to in Article 51 a single identification number for a clinical performance study conducted in one site or multiple sites, in one or more than one Member State. The sponsor shall use this single identification number when registering the clinical performance study in accordance with Article 50.[16]

2. The sponsor of a clinical performance study shall submit [17] […] an application to the Member State(s) in which the study is to be conducted accompanied by the documentation referred to in Annex XIII. [18] […] Within ~~six days~~ **ten days** [19] [20] [21] [22] [23] after receipt of the application, the Member State concerned shall notify the sponsor whether the clinical performance study falls within the scope of this Regulation and whether the application is complete.

Where the Member State has not notified the sponsor within the time period referred to in the first subparagraph, the clinical performance study shall be considered as falling within the scope of this Regulation and the application shall be considered complete. [24] [25]

---

16 **MD Proposal** : Delete "*Before making the first application, the sponsor shall procure from the electronic system referred to in Article 51 a single identification number for a clinical performance study conducted in one site or multiple sites, in one or more than one Member State. The sponsor shall use this single identification number when registering the clinical performance study in accordance with Article 50*."

17 **MD Proposal** : Add "*by means of the electronic system referred to in Article 53*"

18 **MD Proposal** : Add "*The electronic system referred to in Article 53 shall generate a union wide unique single identification number for this clinical investigation which shall be used for all relevant communication in relation to the clinical investigation concerned.*"

19 **MD Proposal** : Replace "*six days*" by "*ten days*"

20 AT, CY, DK, EE, ES, FR, IT, NL, PL, PT, SE: Timeline is too short. CZ, LV, SE: Are these calendar or working days? Cion: Calendar days.

21 DE: Replace "*six days*" by "*ten days*". SK: Support.

22 SI: Replace "*six days*" by "*15 days*".

23 FR: Replace "*six days*" by "*18 days*".

24 **MD Proposal** : Delete "*Where the Member State has not notified the sponsor within the time period referred to in the first subparagraph, the clinical performance study shall be considered as falling within the scope of this Regulation and the application shall be considered complete*".

25 SI: Scrutiny reserve on tacit approval.

3. Where the Member State finds that the clinical performance study applied for does not fall within the scope of this Regulation or that the application is not complete, it shall inform the sponsor thereof and shall set a maximum of ~~six days~~ **30 days** [26] [27] for the sponsor to comment or to complete the application.

Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.

Where the Member State has not notified the sponsor according to paragraph 2 within three days [28] […] following receipt of the comments or of the completed application, the clinical performance study shall be considered as falling within the scope of this Regulation and the application shall be considered complete [29] […].

4. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 3.[30] […]

---

[26] DK, EE, ES, FR, IT, NL, PL, PT, SE: Timeline is too short.

[27] DE: Replace "*six days*" by "*30 days*".

[28] **MD Proposal** : Replace "*Where the Member State has not notified the sponsor according to paragraph 2 within three days"* by *"The Member State has to notify the sponsor within ten days*"

[29] **MD Proposal**: Replace "*the clinical performance study shall be considered as falling within the scope of this Regulation and the application shall be considered complete*" by "*whether the clinical performance study is be considered as falling within the scope of this Regulation and the application is completed*".

[30] **MD Proposal :** Replace "*Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 3"* by *"In the period during which the application is being examined the Member State may request, on a single occasion, additional information from the sponsor. The expiry of the deadline pursuant paragraph 5 b) (second indent) shall be suspended from the date of the request until such time as the additional information has been received*".

5. The sponsor may start the clinical performance study in the following circumstances:

   (a) in the case of devices for performance evaluation classified as class C or D, as soon as the Member State concerned has notified the sponsor of its approval;

   (b) in the case of devices for performance evaluation classified as class A or B immediately after the ~~date of application~~ **date of validation**[31], provided that the Member State concerned has so decided and that evidence is provided that the rights, safety and well-being of the subjects to the clinical performance study are protected; [32]

   (c) after the expiry of ~~35 days~~ **60 days**[33] [34] after the validation date referred to in paragraph 4, unless the Member State concerned has notified the sponsor within that period of its refusal based on considerations of public health, patient safety or public policy.

6. Member States shall ensure that the persons assessing the application do not have conflicts of interest and that they are independent of the sponsor, the institution of the study site(s) and the investigators involved, as well as free of any other undue influence.

   Member States shall ensure that the assessment is done jointly by a reasonable number[35] of persons who collectively have the necessary qualifications and experience. In the assessment, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account.[36]

7. The Commission shall be empowered to adopt delegated acts[37] in accordance with Article 85 amending or supplementing, in the light of technical progress and global regulatory developments, the requirements for the documentation to be submitted with the application for the clinical performance study that is laid down in Chapter I of Annex XIII.

---

31 AT: Replace "*date of application*" by "*date of validation*". DE: Support.

32 SE: Delete this subparagraph.

33 AT, CY, DK, EE, ES, FR, IT, LV, NL, PL, PT, SE: Timeline is too short.

34 AT: Replace "*35 days*" by "*60 days*". ES, HU, PT, SE, SI, SK, UK: Support.

35 DK: How many people constitute a reasonable number of persons in this context?

36 NL: Difficult to find a patient with relevant knowledge of this area. PT: Should be representative of the patient from the Ethics Committee; not the patient himself. SK: Patient should be a member of the Ethics Committee

37 AT, CY, DK, ES, SE: Reserve on delegated acts.

Article 50

Registration of [38] […] *interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies*

1. Before commencing the clinical performance study, the sponsor shall enter in the electronic system referred to in Article 51 the following information regarding the clinical performance study:
   (a) the single identification number of the clinical performance study;
   (b) the name and contact details of the sponsor and, if applicable, his contact person[11] established in the Union;
   (c) the name and contact details of the natural or legal person responsible for the manufacture of the device for performance evaluation, if different from the sponsor;
   (d) the description of the device for performance evaluation;
   (e) the description of the comparator(s), if applicable;
   (f) the purpose of the clinical performance study;
   (g) the status of the clinical performance study.

2. Within one week of any change occurring in relation to the information referred to in paragraph 1, the sponsor shall update the relevant data in the electronic system referred to in Article 51.[39]

3. The information shall be accessible to the public, through the electronic system referred to in Article 51 [40] […], unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:
   (a) protection of personal data in accordance with Regulation (EC) No 45/2001,
   (b) protection of commercially sensitive information,
   (c) effective supervision of the conduct of the clinical performance study by the Member State(s) concerned.

---

38 **MD Proposal :** Replace "*Registration of*" by "*Public access to information on*"

39 **MD Proposal :** Delete "*Within one week of any change occurring in relation to the information referred to in paragraph 1, the sponsor shall update the relevant data in the electronic system referred to in Article 51*"

40 **MD Proposal** : Replace "*The information shall be accessible to the public, through the electronic system"* by *"The information referred to in paragraph 1 shall be accessible to the public*".

4. No personal data of subjects participating in the clinical performance study shall be accessible to the public.

Article 51

Electronic system on interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies

1. The Commission shall, in collaboration with the Member States, set up and manage [41] […] an electronic system on interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies to create the single identification numbers for such clinical performance studies [42] […] referred to in Article 49(1) and to collate and process the following information:
   (a) the registration of clinical performance studies in accordance with Article 50;
   (b) the exchange of information between the Member States and between them and the Commission in accordance with Article 54;
   (c) the information related to clinical performance studies conducted in more than one Member State in case of a single application in accordance with Article 56;
   (d) the reports on serious adverse events and device deficiencies referred to in Article 57(2) in case of single application in accordance with Article 56. [43] […]

[41] **MD Proposal** : Replace "*set up and manage*" by "*set up, manage and maintain*"
[42] **MD Proposal** : Add "*and to be used as an entry point for the submission of application*"
[43] **MD Proposal** : Replace " *to collate and process the following information: (a)the registration of clinical performance studies in accordance with Article 50; (b)the exchange of information between the Member States and between them and the Commission in accordance with Article 54; (c) the information related to clinical performance studies conducted in more than one Member State in case of a single application in accordance with Article 56; (d)the reports on serious adverse events and device deficiencies referred to in Article 57(2) in case of single application in accordance with Article 56*" by "*for all other submission of data, for the exchange of information relating to clinical [investigations] in accordance with this Regulation between the Member States and between them and the Commission, and for reporting on serious adverse events and device deficiencies referred to in Article 59*" .

2. When setting up the electronic system referred in paragraph 1, the Commission shall ensure that it is interoperable with the EU database for clinical trials on medicinal products for human use set up in accordance with Article […] of Regulation (EU) No [Ref. of future Regulation on clinical trials]. With the exception of the information referred to in Article 50, the information collated and processed in the electronic system shall be accessible only to the Member States and to the Commission.

3. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 determining which other information regarding clinical performance studies collated and processed in the electronic system shall be publicly accessible to allow interoperability with the EU database for clinical trials on medicinal products for human use set up by Regulation (EU) No [Ref. of future Regulation on clinical trials]. Article 50(3) and (4) shall apply.

Article 52

Interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies with devices authorised to bear the CE marking

1. Where a clinical performance study is to be conducted to further assess devices which are authorised in accordance with Article 40 to bear the CE marking and within its intended purpose referred to in the relevant conformity assessment procedure, hereinafter referred to as 'post-market follow-up performance study', the sponsor shall notify the Member States concerned at least 30 days prior to their commencement if the study would submit subjects to additionally invasive or burdensome procedures. [44] […] Articles 48(1) to (5), 50, 53, 54(1) and 55(1), the first subparagraph of Article 55(2) and the relevant provisions of Annexes XII and XIII shall apply.

[44] **MD Proposal** : Add "*The notification shall be made by means of the electronic system referred to in Article 53. It shall be accompanied by the documentation referred to in …*"

2. If the aim of the clinical performance study regarding a device which is authorised in accordance with Article 40 to bear the CE marking is to assess such device for a purpose other than that referred to in the information supplied by the manufacturer in accordance with Section 17 of Annex I and in the relevant conformity assessment procedure, Articles 48 to 58 shall apply.

Article 53[45] [46]

Substantial modifications to interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies

1. If the sponsor introduces [47] […] modifications to a clinical performance study that are likely to have a substantial impact on the safety or rights of the subjects or on the robustness or reliability of the clinical data generated by the study, he shall notify [48] […] the Member State(s) concerned [49] […] of the reasons for and the content of those modifications. The notification shall be accompanied by an updated version of the relevant documentation referred to in Annex XIII [50] […].

2. The sponsor may implement the modifications referred to in paragraph 1 at the earliest 30 days after notification, unless the Member State concerned has notified the sponsor of its refusal based on considerations of public health, patient safety or public policy [51] […].

---

45 **DM Proposal** : Introduce an article "Modifications…" prior to the article "Substantial modifications…"

46 **DM Proposal** : Add " *Art. 55* ***Modifications to a clinical [investigation]*** *- The sponsor shall notify the Member State(s) concerned any changes made to the documents submitted pursuant to Article 51 paragraph 1 after having received an approval or favourable opinion pursuant Article 51 paragraph 5. The notification shall by made by means of the electronic system referred to in Article 53. The changed documents shall be attached to the notification and the changes shall be marked.*"

47 **MD Proposal** : Replace "*introduces*" by "*intends to introduce*"

48 **MD Proposal** : Add "*by means of the electronic system referred to in Article…*"

49 **MD Proposal** : Add "*and the Ethics committee concerned*"

50 **MD Proposal** : Add "*changes shall be marked.*"

51 **MD Proposal** : Replace "*of public health, patient safety or public policy*" by "*according to Article 51a paragraph 4 or the Ethics committee concerned has refused a favourable opinion based on grounds according to Article 51c paragraph 4.*"

Article 54

Information exchange between Member States on interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies

1. Where a Member State has refused, suspended or terminated a clinical performance study, or has called for a substantial modification or temporary halt of a clinical performance study, or has been notified by the sponsor of the early termination of a clinical performance study on safety grounds, that Member State shall communicate its decision and the grounds therefor to all Member States and the Commission by means of the electronic system referred to in Article 51.

2. Where an application is withdrawn by the sponsor prior to a decision by a Member State that Member State shall inform all the other Member States and the Commission of that fact, by means of the electronic system referred to in Article 51.

Article 55

Information by the sponsor in the event of temporary halt or termination of interventional clinical performance studies or of other clinical performance studies involving risks for the subjects of the studies

1. If the sponsor has temporarily halted a clinical performance study on safety grounds, [52] […] he shall inform the Member States concerned within 15 days of the temporary halt [53] […].

2. The sponsor shall notify each Member State concerned of the end of a clinical performance study in relation to that Member State, providing a justification in the event of early termination. [54] That notification shall be made within 15 days from the end of the clinical performance study in relation to that Member State.

---

[52] **MD Proposal** : Add "*or has early terminated a clinical [investigation],* "

[53] **MD Proposal** : Add "*or early termination, providing a justification.*"

[54] **MD Proposal** : Delete "*providing a justification in the event of early termination"*

If the study is conducted in more than one Member State, the sponsor shall notify all Member States concerned of the overall end of the clinical performance study. That notification shall be made within 15 days from the overall end of the clinical performance study.

3. Within one year from the end [55] […] of the clinical performance study, the sponsor shall submit to the Member States concerned a summary of the results of the clinical performance study in form of [56] a clinical performance study report referred to in Section 2.3.3 of Part A of Annex XII. Where, for scientific reasons, it is not possible to submit the clinical performance study report within one year, it shall be submitted as soon as it is available. In this case, the clinical performance study protocol referred to in Section 2.3.2 of Part A of Annex XII shall specify when the results of the clinical performance study are going to be submitted, together with an explanation.

Article 56

Interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies conducted in more than one Member State[57]

1. By means of the electronic system referred to in Article 51, the sponsor of the clinical performance study to be conducted in more than one Member State may submit, for the purpose of Article 49, a single application that, upon receipt, is transmitted electronically to the Member States concerned.

---

55 **MD Proposal** : Add "*or early termination*"

56 **MD Proposal** : Delete "*a summary of the results of the clinical performance study in form of*"

57 **MD Proposal** :
1) Start with mandatory Coordinated Assessment Procedure (CAP), but stretching gradually its content over time
2) Start with voluntary CAP for a certain time, collect experience, then report by the Commission on its functioning and, after positive experience, delegated/implementing act of the Commission on mandatory CAP, maybe with appropriate modifications;

2. In the single application, the sponsor shall propose one of the Member States concerned as coordinating Member State. If that Member State does not wish to be the coordinating Member State, it shall agree, within six days of submission of the single application, with another Member State concerned that the latter shall be the coordinating Member State. If no other Member State accepts to be the coordinating Member State, the Member State proposed by the sponsor shall be the coordinating Member State. If another Member State than the one proposed by the sponsor becomes coordinating Member State, the deadlines referred to in Article 49(2) shall start on the day following the acceptance.

3. Under the direction of the coordinating Member State referred to in paragraph 2, the Member States concerned shall coordinate their assessment of the application, in particular of the documentation submitted in accordance with Chapter I of Annex XIII, except for Sections 4.2, 4.3 and 4.4 thereof which shall be assessed separately by each Member State concerned. [58]

[58] **MD Proposal :** Delete **"** *Under the direction of the coordinating Member State referred to in paragraph 2, the Member States concerned shall coordinate their assessment of the application, in particular of the documentation submitted in accordance with Chapter I of Annex XIII, except for Sections 4.2, 4.3 and 4.4 thereof which shall be assessed separately by each Member State concerned*"

The coordinating Member State shall:

(a) within 6 days [59] […] of receipt of the single application notify the sponsor whether the clinical performance study falls within the scope of this Regulation and whether the application is complete, except for the documentation submitted in accordance with Sections 4.2, 4.3 and 4.4 of Chapter I of Annex XIII for which each Member State shall verify the completeness. Article 49(2) to (4) shall apply to the coordinating Member State in relation to the verification that the clinical performance study falls within the scope of this Regulation and that the application is complete, [60] […] except for the documentation submitted in accordance with Sections 4.2, 4.3 and 4.4 of Chapter I of Annex XIII. [61] […] Article 49(2) to (4) shall apply to each Member State in relation to the verification that the documentation submitted in accordance with Sections 4.2, 4.3 and 4.4 of Chapter I of Annex XIII is complete;

(b) establish the results of the coordinated assessment in a report to be taken into account by the other Member States concerned when deciding on the sponsor's application in accordance with Article 49(5). [62] […]

---

59 **MD Proposal :** Replace **"***6 days" by " ten days"*

60 **MD Proposal :** Add **"** *having taken into account considerations expressed by the other Member States concerned*,"

61 **MD Proposal :** Add **"** *Concerned Member States may communicate to the reporting Member State any considerations relevant to the validation of the application within seven days from the submission of the application.*"

62 **MD Proposal :** Replace "*establish the results of the coordinated assessment in a report to be taken into account by the other Member States concerned when deciding on the sponsor's application in accordance with Article 49(5).*" by "*The Commission may, by means of implementing acts, set out the procedures and timescales for a coordinated assessment led by the coordinating competent authority that shall be taken into account by concerned Member States when deciding on the sponsor's application. Such implementing acts may also cover the procedures for coordinated assessment in the case of substantial modifications pursuant to paragraph 4 and in the case of reporting of events pursuant to Article 59(4). Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(3).*"

4. The substantial modifications referred to in Article 53 shall be notified to the Member States concerned by means of the electronic system referred to in Article 51. Any assessment as to whether there are grounds for refusal as referred to in Article 53 shall be carried out under the direction of the coordinating Member State. [63] […]

5. For the purpose of Article 55(3), the sponsor shall submit the clinical performance study report to the Member States concerned by means of the electronic system referred to in Article 51.

6. The Commission shall provide secretarial [64] […] support to the coordinating Member State in the accomplishment of its tasks provided for in this Chapter.

Article 57

Recording and reporting of events occurring during interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies

1. The sponsor shall fully record any of the following:
   (a) an adverse event identified in the clinical performance study protocol as critical to the evaluation of the results of the clinical performance study in view of the purposes referred to in Article 48(1);
   (b) a serious adverse event;
   c) a device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
   (d) new findings in relation to any event referred to in points (a) to (c).

[63] **DM Proposal :** Replace "*Any assessment as to whether there are grounds for refusal as referred to in Article 53 shall be carried out under the direction of the coordinating Member State." by "The Member States concerned shall assess as to whether there are grounds for refusal as referred to in Article 55 and notify the sponsor accordingly* "

[64] **MD Proposal :** Replace *" secretarial* " by "*administrative*"

2. The sponsor shall report to all Member States where a clinical performance study is conducted without delay any of the following[65] […] :

   (a) a serious adverse event that has a causal relationship with the device for performance evaluation, the comparator or the study procedure or where such causal relationship is reasonably possible;

   (b) a device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

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

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

3. The sponsor shall also report to the Member States concerned any event referred to in paragraph 2 occurring in third countries in which a clinical performance study is performed under the same clinical performance study protocol as the one applying to a clinical performance study covered by this Regulation.

4. In the case of a clinical performance study for which the sponsor has used the single application referred to in Article 56, the sponsor shall report any event as referred to in paragraph 2 by means of the electronic system referred to in Article 51. Upon receipt, this report shall be transmitted electronically to all Member States concerned.

   Under the direction of the coordinating Member State referred to in Article 56(2), the Member States shall coordinate their assessment of serious adverse events and device deficiencies to determine whether a clinical performance study needs to be terminated, suspended, temporarily halted or modified.

---

[65] **MD Proposal:** Add "*, by means of the electronic system referred to in Article 51:"*

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

5. In the case of post-market follow-up performance studies referred to in Article 52(1), the provisions on vigilance contained in Articles 59 to 64 shall apply instead of this Article[66] […].

Article 58

Implementing acts

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

(a) harmonised forms for the application for clinical performance studies and their assessment as referred to in Articles 49 and 56, taking into account specific categories or groups of devices;
(b) the functioning of the electronic system referred to in Article 51;
(c) harmonised forms for the notification of post-market follow-up performance studies as referred to in Article 52(1), and of substantial modifications as referred to in Article 53;
(d) the exchange of information between Member States as referred to in Article 54;
(e) harmonised forms for the reporting of serious adverse events and device deficiencies as referred to in Article 57;
(f) the timelines for the reporting of serious adverse events and device deficiencies, taking into account the severity of the event to be reported as referred to in Article 57.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 84(3).

---

[66] **MD Proposal :** Add "*unless a causal relationship between the serious adverse event and the preceding investigational procedure has been established*."