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NOTE

From:	General Secretariat of the Council
To:	Working Party on Pharmaceuticals and Medical Devices
No. prev. doc.:	16182/14 PHARM 98 SAN 456 MI 957 COMPET 653 CODEC 2384
No. Cion doc.:	14493/12 PHARM 71 SAN 215 MI 597 COMPET 600 CODEC 2305 + COR 1
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 - *Chapter VI and Annexes*

Delegations will find attached texts containing proposals for changes to the Proposal for a Regulation on medical devices prepared by the Latvian Presidency. The texts are based on document 16182/14. These texts are intended as bases for the examination of the Proposal at the meeting of the Working Party on 12 and 13 February 2015.

Annex A to this Note sets out the text of Chapter VI.

Annex B to this Note sets out the text of definitions to be examined on 12 and 13 February.

Annex C to this Note sets out the text of Annex XIII to the Proposal.

Annex D to this Note sets out the text of Annex XIV to the Proposal.

Text conventions

Additions of new text to the text in the Commission proposal are set out in ***bold italics***.

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

Deletions of text in previous Presidency documents are set out in ***bold italics strikethrough***.

Changes compared to document 16182/14 are highlighted in grey.

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Chapter VI

Clinical evaluation and clinical investigations

Article 49

Clinical evaluation

1. ***Confirmation of conformity with the requirements concerning the characteristics of safety and performances referred to in ~~Section 1 of~~ Annex I and where applicable ~~other~~ relevant***[1] ***requirements of Annex IIa***[2] ***under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit/risk ratio referred to in Sections 1 and 5 of Annex I, shall be based on clinical data providing sufficient clinical evidence.*** [3] [4] [5]

The manufacturer shall specify[6] ***and justify the ~~level of~~***[7] ***clinical evidence provided as being ~~necessary~~ sufficient***[8] ***to demonstrate compliance with the relevant essential requirements on safety and performance. ~~which shall correspond to~~ The level of evidence ~~should~~ shall be ~~proportionate~~ adequate***[9] ***to the clinical risk of the device, the specified claims of the manufacturer***[10] ***and with consideration of the characteristics of the device and its intended purpose.***[11]

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1 **AT** replace "*other*" with "*relevant*".

2 **PT** insert "*safety*", **Cion** Support. **Cion** add "*performance requirements*" "*and where applicable other requirements of Annex II*" delete "*sufficient*"
DS 1488/14 LT The provisions of Chapter 6 must be in line with the relevant Annexes XIII and XIV. Chapter 6 (rather than Annexes) must cover general requirements applied for the clinical evaluation and clinical investigation.

3 First sentence is moved from Annex XIII. **AT** support,

4 **1312/14 FR** suggest text from **DS 1245/13 UK** suggestion.

5 **DK** Simplify the text.

6 **DS 1560/14 AT** delete "*document*", reinstate "*specify*"

7 **DS 1560/14 AT** delete "*level of*". PT support. DE,ESP necessary to clarify.

8 **AT** replace "*necessary*" with "*provided as being sufficient".*

9 **DS 1560/14 AT** replace "*proportionate*" with "*adequate*" IE: support.

10 **DS 1560/14 AT** add "*the specified claims of the manufacturer*"

11 **UK** Replace this paragraph in accordance with DS 1345/13, **DE, ES, FR, PT** Support. Cion: Agreed with this approach. **SE:** Add "*to support the assessment of conformity of the device*". **IE** add "*The level of evidence should be proportionate to the clinical risk of the device and with consideration o*f ".

~~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.[12]

2. A clinical evaluation shall follow a defined and methodologically sound procedure based on ~~***either of***~~[13] 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***~~ [14] of the device, where the following conditions are satisfied:

   - it is demonstrated that the device ***and its use***[15]subject to clinical evaluation and the device to which the data relate are equivalent[16] ***in accordance with section A of Annex XIII***,
   - the data adequately demonstrate compliance with the relevant general safety and performance requirements[17];

   (b) a critical evaluation of the results of all clinical investigations***, with a preference given to those***[18] performed ***in the EU Member States or Countries that comply with the European regulations***[19] 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)[20].

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12 **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** supports.

13 **DK, LT, AT, FI** add "*either of*". **DE, IE, AT, SE, UK, Cion** disagree.

14 **DS 1385/14 NL** delete "*and its use*" **DK, DE** support; **Cion** disagrees.

15 Reinstated following the WP on 27 and 28 October. **NL, DE, PT** disagree.

16 **DS 10451/13 DE**: 'Equivalent' should be defined; **FR, PT** support.

17 **DS 1002/14 DE** add "*in respect to technical, biological and clinical characteristics, including usability in the intended context of use*". **DS 1312/14 FR** opposed to this addition.

18 **10451/13 AT** add "*, with preference to those*" **IT, PT** supports; **DK, PL, SE, UK** disagree; **IE, AT** support addition "*it should be evaluated only the investigations made in the EU MS or Countries that comply with the European regulations*".

19 **IE** it should be evaluated only the investigations made in the EU MS or Countries that comply with the European regulations"; **AT** support; **NL** disagrees; **DK** need to clarify the meaning **AT, UK** support, **UK** add "*given to* ".

20 **DS 1560/14 AT** delete paragraph (c) as "*either of*" has been deleted.

(d) [21] ***a ~~comparison~~ consideration of currently available alternative ~~between the device and other~~ treatments ~~options~~ for that purpose ~~employed in the current clinical practice~~, if any.*** [22]

2a. [23] ***In the case of implantable devices and devices falling within class III, clinical investigations shall be performed except if the device has been designed by modifications of a device already marketed by the same manufacturer if the modifications have been demonstrated by the manufacturer and accepted by the Notified Body ~~as non-substantial that are~~ as being*** [24] ***equivalent in accordance to section A Annex XIV, to the marketed device and the clinical evaluation is sufficient to demonstrate conformance to the relevant safety and performance requirements. In this case the Notified Body shall check that the PMCF plan is appropriate ~~to confirm that the benefit/risk ratio is not affected~~ and includes post market studies to demonstrate the safety and performance of the device.*** [25] [26]

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[21] **Pcy** has tried to find a *softer* wording that could serve as a compromise.

[22] **CZ, DK, ES, NL, PL, UK** delete d). **DE, IE, FR, NL, AT, PT, SE** disagree deletion.

[23] ~~**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."~~

[24] **DS 1560/14 AT** replace "*that are*" by "*as being*"

[25] **DK** 'disagree' **DE, ES, AT, PT, UK** define *"non-substantial"*; **IE** add *"and the clinical evaluation is sufficient to demonstrate conformance to the relevant safety and performance requirements. ……in this case the Notified Body shall check that the PMCF plan is appropriate and includes post market studies to demonstrate the safety and performance of the device.* **NL** supports.
Suggested text from **DS 1312/14 FR**. **DE, IE, ES, LT, AT, PT, UK, Cion** support; **DK** disagree.

[26] **DS 1482/14 SE** replace paragraph 2a with *"In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.*".
NL replace paragraph 2a with "*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*"; **DE, ES, SE, Cion** simplify the text; **DK** clinical investigation is not always necessary for Class III medical devices.

3. ***Except for class III and implantable devices, w***here demonstration of conformity with general safety and performance requirements based on clinical ~~data~~ ***evidence***[27] 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 ***clinical*** data obtained from the implementation of the manufacturer's ***PMCF according to Annex XIII Part B and***[28] ***the*** post-market surveillance plan referred to in Article 8(6).

For devices classified as class III and implantable devices, the PMCF report, and if appropriate, the[29] ***summary of safety and clinical performance referred to in Article 26(1) shall be updated at least annually with these data.***[30]

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27 **DE**, **ES** reintroduce "*data* " delete "*evidence*" **AT, PT, SE** add *"evidence"*. **DS 1488/14 LT** The provisions (in point 3) are in conflict with new 49.1 which states that clinical evidence is mandatory in all cases. Therefore the text "where…. Clinical evidence is not deemed appropriate" is not clear. In our opinion clinical evidence is necessary in all cases. We would suggest to delete the word "where" and define when it is not necessary to do clinical evaluation as it is defined in Article 49(2).

28 **AT** add "*clinical data obtained from the implementation of the manufacturer's PMCF according to Annex XIII Part B and*".

29 **DS 1560/14 AT** add "*PMCF report, and if indicated, the*"

30 **DK, SE** "*annually*" is excessive, **DK, DE** "*annually*" is excessive**,** prefer "*when necessary*" **IE** support "*annually***" 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.***" ES, FR, HU, PT** support – **DS 1345/13 UK - DS 1519/13 IT - DS 1312/14 FR - DS 1385/14 NL** "This relates to PMS requirements and the annually reports on all PMS data, including PMCF. When requirements on PMS and the annual report are clear, this section is not necessary".

5. The clinical evaluation***, its results*** and ~~its outcome~~ ***the clinical evidence derived from it***[31] 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*** the technical documentation referred to in Annex II relating to the device concerned. ***The clinical evaluation report shall be made publicly available.***[32]

6. [33] ***Where necessary to ensure the uniform application of Annex XIII*** ~~***In the light of technical progress***~~ ~~***and the state of the art***~~***,*** ~~***in order to assure a homogeneous interpretation of Annex XIII,***~~ ***the Commission may,*** **having due regard to** ***technical and scientific progress,*** ~~***shall be empowered to***~~ ***adopt*** ~~***delegated***~~[34] ***implementing acts*** ~~***in accordance with article 89 complementing or supplementing the clinical evaluation and post market clinical follow up procedures set out in Annex XIII.***~~

~~***It is of particular importance that the Commission carry out consultations with experts, including Member States' experts, before adopting those delegated acts.***~~ ***Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88 (3).***

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[31] **DS 1488/14 LT** the text should be in line with the provisions of Annex XIII, Part 6.

[32] **DS 1482/14 SE** add "*The clinical evaluation report shall be made publicly available.*" at the end of 49(5).

[33] **DS 1312/14 FR**. **ES, AT** support.

[34] **DS 1482/14 SE** reinstate "*delegated*".

Article 50

General requirements regarding clinical investigations

1. [35] [36]Clinical investigations ~~shall be subject to ***scientifically valid and***~~ ***shall be designed, conducted, authorized,***[37] ***recorded and reported in accordance with the provisions of*** Articles 50-60 and Annex XIV ~~***such that the clinical data generated will be reliable and robust***~~[38] if they are conducted for one or more of the following purposes:

   (a) to ~~***examine***~~ ***establish***[39] ***or*** 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 ***sponsor*** ~~manufacturer~~;

   (b) to ~~***examine***~~ ***establish***[40] ***or*** verify ~~that devices achieve~~ the ~~intended~~ benefits ***of the device for*** ~~to~~ the patient as specified by the ***sponsor*** ~~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.

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[35] **DK, IE, AT, PT** agree. **DE** reserve on "*examine*". **DK** add "*be*". **AT, FR** replace "*manufacturers*" with "*sponsor*". **IE, UK**, "scientific validity" relevant concept, it should be expressed. **IE** proposes a rewording including also 50.4,. **AT** support
DS 1488/14 LT In new Article 49(1) there is a link to Annex 1, therefore the provisions of parts a-c repeat provisions already defined in Annex 1. Lithuania is not in favour to broaden the scope (currently it is in conflict with Article 1) We would support the proposal for the separate N.M.C.I legislation

[36] **DS 1482/14 SE** change proposed text to "*Clinical investigations shall be designed and conducted <u>in accordance with the latest scientific knowledge and</u> recorded and reported in accordance with the provisions of Articles 50-60 and Annex XIV if they…*".

[37] **Cion** add "*authorized*".

[38] **Pcy** sentence moved to paragraph 3.

[39] **Cion** delete "*examine*" add " *establish*".

[40] **Cion** delete "*examine*" add " *establish*".

2. Where the sponsor ***of a clinical ~~trial~~ investigation*** is not established in the Union, ~~he~~ ***that sponsor*** shall ensure that a ~~contact~~ ***natural or legal*** ~~person~~ ***representative***[41] is established in the Union ***as its legal representative***. ~~That contact person~~ ***Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and*** shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that ~~contact person~~ ***legal representative*** shall be ***deemed to be a*** ~~considered as~~ communication to the sponsor.[42]

Member States may choose not to apply ~~paragraph 1~~ the subparagraph above as regards clinical investigation to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical investigation who shall be the addressee for all communications with the sponsor provided for in this Regulation.[43]

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41 **DS1385/14 NL** replace "*person*" with "representative".

42 **DS 1385/14 NL** prefer the text from the CTR, art. 74
DE, IE, AT, Cion support. **UK** add "*paragraph 2 art74 CTR*".
DK p.2 prefer text from Cion proposal, **ES, HR, HU, AT, Cion** support Presidency proposal.
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**.

43 **DE, FR, PT, Cion** second paragraph of point 2 redundant.

3. [44] Clinical investigations shall be designed and conducted ~~***under consideration of the principles of the Declaration of Helsinki***~~[45] ***in accordance with the principles set out in Annex XIV,*** in a way that the rights, safety***, dignity*** and well-being of the subjects participating in a clinical investigation are protected and ***prevail over all other interests and the clinical data obtained are going to be scientifically valid, reliable and robust***[46]

~~***It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results. An ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects going beyond ethics, as appropriate for each Member State concerned.***~~

~~***Clinical investigations shall be designed and conducted in accordance with the principles of scientific integrity and validity and in a way*** that the clinical data generated in the clinical investigation are going to be reliable and robust.~~[47]

~~4. Clinical investigations shall be designed, conducted, recorded and reported in accordance with the provisions of Articles 50 to 60 and of Annex XIV.~~[48]

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[44] **DS 1479/14 FR, AT** complete sentence with "*dignity*" **Cion** support "*harmonize similar expression thought the draft text*" **DK, IE**, "*harmonize with Annex XIV*" **IE, UK** delete p.3 last 2 sentences, ~~**DE, ES, NL, UK** reference to the declaration of Helsinki should not be incorporated into this article, **Cion** support **SE** agree reference to the declaration of Helsinki.~~

[45] ~~**FR, AT** disagree deletion.~~

[46] **Pcy** addition from paragraph . **DS 1479/14 AT** Copy out of Directive 93/42/EEC, Annex X. **Cion** avoid repetition of Annex XIV.

[47] **PT** disagrees deletion.

[48] **DK,** reintroduce p.4 , **HU, AT** support . **DS 1479/14 AT** Text recovered and inserted in p.1.

5. A clinical investigation according to paragraph 1 may be conducted only where all of the following conditions are met: [49] [50]

(a) the clinical investigation was subject to an authorisation by a competent authority of the Member State(s) concerned, in accordance with Art.51 paragraph 5 [51] ***of this Regulation, ~~unless otherwise stated by national provisions~~*** [52]***,***

(b) an independent Ethics Committee, set up according to national law, has issued a favourable opinion on the planned clinical investigation which, in accordance with the law of the additional Member State Concerned, is valid for that entire Member State [53]***;***

(c) the sponsor, ~~or~~ its legal representative or a contact person pursuant to paragraph 2, [54] ***is established in the Union;*** [55]

~~(ca) the principles of the Declaration of Helsinki are observed;~~

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[49] **DS 1385/14 NL** Question: to whom are these provisions addressed? Responsibilities should be very explicit.

[50] **BE, DK, BU** general scrutiny reserve, **BE, DK, BU, UK, ES, FI** too detailed**.**
FR "*unless otherwise stated*" asks for clarification on the meaning **DE** "*unless otherwise stated*" may be useful in case of investigations of low risk MD .
FR delete 50.c) ca) **DK, DE, IE, FR** delete "50.f) **DE** announces written proposal.
DS 1488/14 LT Article 50(5) needs close revision. There are some repetitions of already existed provisions (for example point c which is already set out in 50.2); not clear terminology is used (for example, point a refers to "authorisation by a **competent authority**", meanwhile Article 51.4 refers to validation and evaluation of application according to the proposal done by **Member State**. The provisions of "authorisation" are not defined.
Point f needs amendment: unclear phrase "the conditions under which it is to be conducted";
Point g is unclear in content.
As the processes are different in Member States, we would suggest that the authorisation should be granted by Member State, not defining the specific institution of the Member State. We would suggest to clearly stress that authorisation to perform a clinical investigation would therefore be contained in a single administrative decision by each Member State and that the favourable opinion of ethics committee would be issued within the timelines for the authorisation of that clinical trial."
DK, IE, UK delete 50(g).

[51] **AT DS 1560/14** add "*Art.51 paragraph1 of*".

[52] **AT DS 1560/14** delete "*unless otherwise stated by national provisions*". **DE** Support.

[53] **Pcy** alignment with CTR.

[54] **DS 1560/14 AT** add "or a contact person according to paragraph 2, 2 nd subparagraph"

[55] **DS 1385/14 NL** Align with art. 74 CTR.

(cb) vulnerable populations and subjects are appropriately protected according to Article 50c[56] and relevant national provisions;

(d) the foreseeable risks and inconveniences to the subject are medically justifiable when weighed against the medical device's potential relevance for the subjects and [57] medicine ~~patients~~;

(e) the subject or, where the subject is not able to give informed ~~written~~[58] consent , his or her legal representative has given informed ~~written~~[59] consent in accordance with Article 29 of Regulation (EU) No 536/2014[60].[61]

(f) Provisions for compensation for any damage suffered by a subject resulting from its participation in the clinical investigation are in place in accordance with Article 50.d and the corresponding national provisions, for all MS where the clinical investigation is to be conducted in;[62]

~~(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;

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56 **DS 1560/14 AT** add "*c*", clarification.

57 **DS 1560/14 AT** reinstate "*medicine*", **DE** support, **SE** replace with "*patients*". **AT** replace "*patients*" with "*the subjects*".

58 **NL** delete "*written*".

59 **NL** delete "*written*".

60 OJ L 158/2014 (Clinical trials regulation)

61 **NL DS 1385/14** When we agree on taking up general principles on informed consent, we can also add the requirement that informed consent should be written, as it is also stated in the Clinical Trials Regulation (CTR). **BE** it could be better referring to CTR **NL** support **DK** disagree **PT** agree.

62 **Pcy** reinstated (f) and added Article 50d in analogy with CTR.

(i) ~~*the sponsor has provided an insurance policy, a guarantee or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk 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, covering any damage suffered by a subject resulted from participation in a clinical investigation which also provides compensation when no one else accepts liability for the damage exists;*~~[63]

(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;*~~[64]

(l)[65] ~~*assurance is provided, that*~~ *the investigational device(s) in question conform(s) to the applicable general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the subjects.*[66] *This includes, where appropriate, assurance of technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art.*[67.]

(m) *relevant requirements of Annex XIV are fulfilled*[68].

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[63] **BE, DE, NL, AT, PT, SE** Replace subparagraph (i) with the text from CTR : *"Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk"*; **DK** disagree to replace with CTR text. **FI, UK** redraft subparagraph (i),

[64] Deleted already in DS 1482/14.

[65] Former point (i).

[66] **DS 1479/14 AT** Text by analogy to Directive 93/42/EEC, Annex VIII.

[67] **DS 1479/14 AT** Text put from DS 1002/14 from **DE** with modifications.

[68] **AT** add "*relevant requirements of Annex XIV are fulfilled*".

~~*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.*~~

~~*7. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.*~~

8. The investigator shall be a person, as defined in national law, following a profession which is recognised in the Member State concerned, as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care. Other individuals involved in conducting a clinical investigation shall be suitably qualified by education, training or experience in the relevant medical field and in clinical research methodology,[69] to perform their tasks.[70]

9. The facilities where the clinical investigation is to be conducted shall be similar to the facilities of the intended use and[71] suitable for the clinical investigation.[72]

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[69] **Pcy** introduced from Annex XIV Section I paragraph 2.5 to avoid repetition and the paragraph in Annex is deleted accordingly.

[70] Clinical trials regulation 536/2014 Article 49 Suitability of individuals involved in conducting the clinical trial.

[71] **DS1482/14 SE** add "…*similar to the facilities of the intended use and*…"

[72] Clinical trials regulation 536/2014 Article 50 Suitability of clinical trial sites. **ES** delete.

Article 50a [73] [74]

General requirements regarding clinical investigations not ~~planned for CE marking and commercial purposes~~ covered by Article 50(1) [75]

1. ***Clinical investigations, not covered by Article 50(1), ~~not planned for CE marking and commercial purposes~~*** [76] ***shall be designed, conducted, recorded and reported in accordance with the provisions ~~of paragraphs 2 to 5~~ of Article 50 paragraphs 2, 3, 5b, c, cb, e, f, h and l, 8 and 9 and Article 52 of this Regulation.***

2. ***In order to protect the ~~health~~ rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of the clinical investigations not covered by Article 50(1), ~~planned for CE marking and commercial purposes~~ each Member State shall define any requirements for notification, validation, assessment and/or authorization for such investigations, as appropriate for each Member State concerned.***

~~***3. Member States shall take appropriate provisions for the protection of the health of subjects in such clinical investigations, under consideration of requirements in Article 50.***~~

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[73] **DS 1479/14 AT** A vast majority of MS wanted non-manufacturer driven investigations to be covered in this regulation by general requirements (scientific, ethical, transparency). **UK, Cion** clarify the title of the article**, DK** agree on the principles relating to non-profit investigations. Scrutiny reserve on the articles, it should be regulated by national provision" **IE, AT, PT, UK** "correct references to other articles of the chapter and provide the registration of such CI" **Cion** support **FR** "art. should be deleted, otherwise correct references **DE** "scrutiny reserve p.3 "

[74] **DK, DE d**elete Article 50a; AT, DE delete paragraph 3.

[75] **AT** replace *„planned for CE marking and commercial purposes"* with „*covered by Article 50(1),*to avoid problems of definition of commercial purposes and of possible overlap, **FR** support

[76] **AT** replace "*not planned for CE marking and commercial purposes*" with "*covered by Article 50(1)*", **FR** support

~~***Article 50b***~~[77] [78] [79]

~~***Informed consent***~~

Article 50c[80]

Protection of vulnerable subjects; emergency situations

In order to specifically protect the rights, safety, ~~health,~~ dignity and well-being ~~and rights~~ of vulnerable subjects in clinical investigations, Member States may take appropriate measures, concerning clinical investigations

(a) on minors,

(b) on incapacitated subjects,

(c) on pregnant and breastfeeding women,

(d) in emergency situations, and/or

(e) on persons in residential care institutions, persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical investigations.

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[77] **DS 1479/14 AT** Text out of CTR.

[78] replaced with reference in Article 50e.
DK disagree "national competence" **DE, FR, AT, PT, UK** in general prefer explain with specific articles of the Regulation the ethical principles set out in the CTR with any appropriate changes. **BE** it could be better to refer to **CTR**, **NL** support

[79] **DE** disagree deletion

[80] **BE, DK** disagree. ~~**FR** "There should be an additional point regarding persons under the protection of justice as stated in article 34 of the regulation on clinical trial" **Cion** reflects the similar points of the CTR, integrate with the persons referred to in Article 34~~.

Article 50d

Damage compensation[81]

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

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

Article 51

~~*Application for*~~ ***Notification of a***[82] *clinical investigation*

~~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.~~[83]

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81 **Pcy** by a request of several MS, article inserted by analogy with the CTR.

82 **DS 1482/14 SE** replace "*application*" with "*notification*" throughout this regulation; **AT** support.

83 **DE, HR, Cion** agree deletion p1.

2. [84]The sponsor of a clinical investigation shall submit ***by means of the electronic system referred to in Article 53***[85] ~~an application~~ ***a notification*** 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.*** Within ~~six~~ ***fifteen***[86] days after receipt of the ~~application~~, ***notification*** the Member State concerned shall notify the sponsor whether the clinical investigation falls within the scope of this Regulation and whether the ~~application~~ ***notification*** 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.~~[87] [88]

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84 **UK** harmonize article with CTR, **DE** support **DS 1488/14 LT** "The process of the validation/authorisation must be revised. The meaning of "whether the application is complete" is not clear. If evaluation of the completeness means that all required documents are submitted, we would suggest to add "whether the application is complete in accordance with Chapter II of Annex XIV". However, in our opinion validation date should not mean the authorisation/approval. If so, the time for the evaluation of the application is too short. Different terminology used in the text: validation date, approval, authorisation needs more specification."

85 **DK** doubts about the financial burden of electronic system

86 **FR** prefer 10 days and not 15**, p.3** 10 days not 30**. UK "**standardize the timing to CTR. **FI, AT,DE,ES** agree 15 days**, DK "**not sure that the time is sufficient"p.3 agree 30 days not 6. SE agree 30 days but prefer 40 days
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. **DE**: Replace "*six days*" by "*ten days*". **SK:** Support. **SI**: Replace "*six days*" by "*15 days*". **FR**: Replace "*six days*" by "*18 days*.
FR: Replace "*six days*" by "5 *days*. **AT: Replace "**35 days" by "60 days**". ES, HU, PT, SE, SI, SK, UK:** Support.
SK, SI, CZ, **ES, AT:** Replace "ten *days*" by "*15 days*" **FR, UK IE, HR, DE** align timing with that in CTR. **DS 1385/14 NL** replace "*15 days*" with "*10 days*"

87 **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.

88 **UK** reinstate second subparagraph.

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~~ ***notification*** is not complete, it shall inform the sponsor thereof and shall set a maximum of ~~six~~ ***30*** [89] days for the sponsor to comment or to complete the ~~application~~ ***notification***.

Where the sponsor has not provided comments nor completed the ~~application~~ ***notification*** within the time-period referred to in the first subparagraph, the ~~application~~ ***notification*** shall be ***deemed to have lapsed*** ~~considered as withdrawn~~ ~~***rejected***~~. [90] ***Where the sponsor considers the ~~application~~ notification does fall under the scope of the regulation and*** [91] is ***complete but the competent authority does not, the ~~application~~ notification shall be considered as rejected.*** [92]

~~Where t~~ ***T***he Member State has ~~not~~ ***to*** notif***y~~ied~~ the sponsor ~~according to paragraph 2~~ within ~~three~~ ***ten*** days following receipt of the comments or of the completed ~~application~~ ***notification***, ***whether*** the clinical investigation ~~shall be~~ ***is*** considered as falling within the scope of this Regulation and the ~~application~~ ***notification*** ~~shall be considered~~ ***is*** complete***d***. [93]

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.~~ ***notification*** ~~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.~~

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89 **FR, UK** replace "*30 days*" with "*10 days*".

90 **IE** Replace "rejected" by "withdrawn" **PT** support, **DE** prefer "rejected"

91 **AT** add „*does fall under the scope of the regulation and"* as scope and completeness are the two main issues of the validation

92 **PT, FI, SE** replace "rejected" **FR** "deemed to have lapsed" **DE, IE** add "*Where the sponsor considers the application is complete but the competent authority does not , the application shall be considered as rejected*"
IE Replace "*rejected*" by "*withdrawn*" **PT** support, **DE** prefer "*rejected*"
BE, FR, UK harmonize timeline with CTR.

93 **UK** supports Cion proposed text.

4a. In the period during which the ~~application~~ notification is being ~~examined~~ assessed[94] the Member State ~~Competent Authority~~[95] 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 first request until such time as the additional information has been received.[96] [97]

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[94] **AT** replace "examined with assessed

[95] **NL DS 1385/14** add "concerned Ethics Committee". **DS 1479/14 AT** There may be an independent request by the relevant ethics committee aside the CA, concerning information relevant to the EC
Pcy proposes to reinstate "*Member State*" with analogy to the CTR – leaving MS the decision making freedom for allowing NCA and/or ethics committees to request information.

[96] **NL** "introduce a provision in case of no response of the sponsor" **ES** support**. IE** *disagree "*only one opportunity to" **Cion** "appropriate to consider the possibility of multiple requests and limit the time according to that of the first request".
ES agree **DK** "*clock stop*" *only for 5b* **IE** *disagree "*only one opportunity to request information, **AT, Cion** support. **DE** Useful the provision of a single request otherwise the procedures may take too long.
IE disagrees "*on a single occasion*".

[97] **DS 1385/14 NL** Replace paragraph 4a with the text "*In the period during which the application is being examined the Member State or the concerned Ethics Committee 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 investigation in the following circumstances:[98]

(a) [99]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~~***, unless otherwise stated by national provisions, immediately after the*** ~~***validated***~~ ***validation***[100] ***date of*** ~~***application***~~ ***notification described in paragraph 4, and***[101] ***provided that the competent Ethics committee in the Member State concerned has issued a favourable opinion which, in accordance with the law of the Member State concerned, is valid for that entire Member State***[102];[103]

(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 which, in accordance with the law of the Member State concerned, is valid for that entire Member State***[104]***, or***

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98 **HR** p.3 30 days may be excessive, agree 4a**, ES** agree 30 days, 5a **DE, AT** 30 days may be prolonged **IE** p5a there are some II class devices that may require evaluations time-consuming and complex because they are very innovative."
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.
CY, DK, EE, ES, FR, IT, NL, AT, PL, PT, SE Timeline is too short**. AT** Replace "*35 days*" by "*60 days*". **ES, HU, PT, SK, SI, SE, UK** Support**.**

99 **ES** I class device should be national competence, **AT** support, **FI** provision too inflexible, **DK, PT, SE** provision may be in contrast to the national law, necessary flexibility"
DE, AT support.

100 **DS 1560/14 AT** replace "*validated*" with "*validation*"

101 **DS 1385/14 NL** delete "*immediately*" add "*and*".

102 **Pcy** alignment with CTR.

103 **DS 1482/14 SE** Delete subparagraph 51.5(a)

104 **Pcy** alignment with CTR.

- ***after the expiry of 60[105] days after the validation date referred to in paragraph 43, 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 ~~notified~~[106] a favourable opinion which, in accordance with the law of the Member State concerned, is valid for that entire Member State*** [107] ~~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 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.~~[108] ~~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.~~

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105 **DS 1482/14 SE** should be prolonged to 90 days in case of coordinated assessment procedure.

106 **Cion** substitute "*issued*" with "*notified*".

107 **Pcy** alignment with CTR.

108 **Deletion p. 6**: Rationale: moved to proposed Article 51a, the involvement of non-scientists and patients is covered by the related articles.

7. The Commission ~~shall be empowered to~~ ***may*** adopt ~~delegated~~[109] ***implementing*** acts in accordance with Article ~~89~~ ***88(3)***[110] ~~amending or supplementing, in the light of technical progress and global regulatory developments,~~ ***in order to assure*** ~~***a homogeneous interpretation***~~ ***the uniform application of*** the requirements for the documentation to be submitted with the ~~application~~ ***notification*** for the clinical investigation that is laid down in Chapter II of Annex XIV.

Article 51a[111] [112] [113]

Assessment by Member States

1. Member States shall ensure that the persons validating and assessing the ~~***application***~~ ***notification , or deciding on it, do not have conflicts of interest, are independent of the sponsor,*** ~~***the investigation site***~~[114] [115]***, the investigators involved and of persons or legal persons financing the clinical investigation, as well as free of any other undue influence.***

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109 **10451/13 CY, DK, ES, AT, SE** Reservation on delegated acts.

110 Reference to paragraph 3 added.

111

	A:Do the delegations agree that items are captured in Regulation?	**B: Do the delegations agree that basic general principles should be fixed in the Regulation?**	**C: Do the delegations prefer that items are regulated exclusively by national provision?**	**SUMMARY**
Assessment by Member States	**BE, CZ, DK, DE, IE, EL, FR, HR, LU, HU, AT, PL, PT, RO, SI, SK, UK**	**BG, EE, IE, ES, CY , LT, NL, FI**	**SE**	**A: 17** **B: 9** **C: 1**

112 **BE, BG, CZ**, **FI, SE** scrutiny reserve **FR** delete 51a) p4 **IE** scrutiny reserve favourable for 51a) 51 d) negative for 51b) 51c) **ES, UK** agree art 51a) but it is too detailed **Cion** agree art 51a) harmonise with art.9 CT art 51d) harmonize with art.67 CTR.

113 **DK** should be regulated in national legislation.

114 **NL** This is a requirement that cannot be implemented. In the Netherlands experts assessing applications are often related to the investigation site. These experts are rare and therefore necessary in the assessment. The most important requirement should therefore be that they have no conflict of interest and that they are independent of the sponsor and other undue influence.

115 **DS 1385/14 NL** delete "*the investigation site*".

2. Member States shall ensure that the assessment is done jointly by a reasonable[116] number of persons who collectively have the necessary qualifications and experience.

3. Member States shall assess whether the clinical investigation is designed in such a way that potential remaining risks to subjects, after risk minimization, are justified, when weighed against the clinical benefits to be expected. They shall examine, under consideration of applicable Common Specifications or harmonized standards, in particular:

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

(b) whether the risk-minimisation solutions employed by the sponsor are described in harmonised standards and, in those cases where the sponsor does not use harmonised standards, the equivalence of the level of protection to harmonised standards;

(c) the plausibility of the measures planned for the safe installation, putting into service and maintenance of the investigational device;

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

(da) relevant requirements of Annex XIV are met.[117]

~~*(e) in the case of products for sterile use, evidence of the validation of the manufacturer's sterilisation procedures or information on the reconditioning and sterilisation procedures which must be conducted by the investigation site;*~~

~~*(f) demonstration of safety, quality and usefulness of any components of animal or human origin or of substances, which may be considered medicinal products according to Directive 2001/83/EC;*~~

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116 **PT** term "reasonable" should be clarified.

117 **AT** add (da) "*relevant requirements of Annex XIV are met.*"

~~*(g) whether the principles of the Declaration of Helsinki and of the provisions on informed consent, according to Article 50d, and of the provisions for the protection of subjects, according to Article 50e (or 50e-g) are met.*~~[118]

4. Member States may refuse the approval of the clinical investigation if:

(a) the clinical investigation does not fall within the scope of this Regulation ~~*as layed down in Article 50 paragraph 1*~~[119]***;***

(b) the ~~*application*~~ ***notification submitted according to Article*** ~~*50*~~ ***51***[120] ***paragraph 3 remains incomplete; (c)*** ~~*no favourable opinion of the*~~ ***an ethics committee*** ~~*concerned*~~ ***has*** ~~*been*~~ ***issued a negative opinion which, in accordance with the law of the Member State concerned, is valid for that entire Member State***[121]***;***

(ca) the medical device or the submitted documents, especially the investigation plan and the investigator's brochure, do not correspond to the latest scientific knowledge, and the clinical investigation, in particular, is not suitable to provide evidence for the safety, performance characteristics or benefit of the medical device on patients, or

(d) the requirements of Article 50 are not met, or

(e) any assessment according to paragraph 3 is negative.

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118 **DE, AT** reinstate subpoints (e),(f),(g)

119 **DS 1560/14 AT** delete "*as layed down in Article 50 paragraph 1*"

120 **DS 1560/14 AT** replace "Article 50" to "Article 51"

121 **Pcy** alignment with CTR.

~~*Article 51b*~~[122] [123] [124]

~~*Ethics Committee*~~

~~*Article 51c*~~[125]

~~*Assessment by the Ethics Committe*~~e

[122]

	A:Do the delegations agree that items are captured in Regulation	B: Do the delegations agree that basic general principles should be fixed in the Regulation?	C: Do the delegations prefer that items are regulated exclusively by national provision?	SUMMARY
Ethics Committee	**DE, IE, EL, FR, HR, LU, HU, AT, PT, RO, SI, SK, SE**	**BG, EE, IE, CY, LV, LT, FI, PL**	**BE, CZ, DK, ES, NL, UK**	**A: 13 B: 8 C: 6**
Assessment by the Ethics Committee	**BE, DE, EL, FR, HR, LU, HU, AT, PL,PT, RO, SK**	**BG, CZ, EE, LV, LT, NL, SI**	**DK, ES, CY, SK, FI, SE, UK**	**A: 12 B: 7 C: 7**

[123] **BE, BG, DK, IE, ES, NL, SE, UK** disagree art 51b) 51 c regarding Ethics Committee). **Cion** support. **FR** delete 51c) **PT** 51c) too detailed, national provision. **AT** agrees on the observations made art 51b) 51 c detail too detailed **DE** Art 51b, 51 c , national laws could be sufficient but it is appropriate to provide uniforms skills of the EC. **DS 1501/14 FI** Article 51b In our view the mandatory involved of patient organisations is not necessary and there should be room for nationally determining the composition of the committee when it also comes to lay members **Article 51c** FI is of the view that procedural details of ethical assessment should be a matter of national provisions.

[124] **DE** basic general principles should be kept.

[125] **DE** basic general principles should be kept.

Article 51d[126] [127] [128]

~~*Corrective measures to be taken by Member States*~~

1. ~~*Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures on its territory:*~~

   ~~*(a) revoke the authorisation of a clinical investigation;*~~

   ~~*(b) suspend a clinical trial;*~~

   ~~*(c) require the sponsor to modify any aspect of the clinical investigation.*~~

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

3. ~~*The Member State concerned shall immediately after taking a measure referred to in paragraph 1 inform all Member States concerned through the EU portal. Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to in paragraph 1.*~~

[126]

	A:Do the delegations agree that items are captured in Regulation ?	**B: Do the delegations agree that basic general principles should be fixed in the Regulation?**	**C: Do the delegations prefer that items are regulated exclusively by national provision?**	**SUMMARY**
Withdrawal, revocation and suspension of the authorization or of the favourable opinion	**BE, DE, IE, EL, FR, HR, CY, LU, HU, AT, PL, PT, RO, SI, SK, UK**	**BG, DK, EE, IE, ES, LT , NL**	**CZ, FI, SE**	**A: 16** **B: 8** **C: 3**

[127] **DS 1479/14 AT, DS 1501/14 FI Article 51d** FI views corrective measures taken by the Member States as a matter best regulated by national provisions. However in particular the list in paragraph 1 should leave room for additional national administrative measures, i.e. not be exhaustive.

[128] **Pcy** Article combined with Article 56 to avoid repetition.

~~*4. The favourable opinion by the relevant ethics committee shall be withdrawn if the Ethics committee subsequently becomes aware that grounds for a refusal pursuant to Article 51 c paragraph 4 existed at the time of issuance; it shall be revoked if the ethics committee subsequently becomes aware of the fact that:*~~

~~*(a) the requirements regarding the suitability of the investigator or of the investigation site are not fulfilled,*~~

~~*(b) the clinical investigation participants are not properly insured*~~

~~*(c) the modalities for selecting clinical investigation subjects do not correspond to the current state of medical knowledge and, in particular, the clinical investigation is unsuitable for proving the safety, performance and functioning of the medical device,*~~

~~*7. If the authorisation to conduct a clinical investigation is withdrawn, revoked or suspended, Member States shall inform by means of the electronic system referred to in Article 53 other affected Member States and the European Commission*~~ **.**

Article 52[129]

*Registration of **a** clinical investigation~~s~~*[130]

1. Before commencing the clinical investigation, the sponsor shall enter[131] ***the following information regarding the clinical investigation*** ~~***which shall be accessible to the public***~~[132] [133] ~~***through***~~ ***in*** the electronic system referred to in Article 53[134] ~~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 or the contact person according to Article 50, paragraph 2***[135] 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.

   (*h*) ***additional data necessary to register a clinical investigation in a public registry which is a primary or partner of, or a data provider to, the WHO ICTRP***[136]

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[129] **Pcy** proposes to delete this paragraph as the mentioned information will be already entered in the electronic system in accordance with Art. 51.2. – reference to Annex XIV Chapter II. Should the MS support adding subparagraph (h), it could be transferred to annex. Alternatively Presidency proposes to request in this Article that the sponsors ensures that the information is updated where necessary.

[130] **DK** "concerns about the introduction of potentially sensitive data"
AT "The EU register should be based on the principles of the International Clinical Trials Registry Platform (ICTRP) of WHO to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base." **PT, IE** support, **NL**, **Cion** prefer original text **PT p1.** Introduce **h)** the principal investigator/s

[131] **DE** necessary to avoid double input of data. **PT, Cion** agrees.
NL DS 1385/14 support **DS 1488/14 LT** We would suggest to indicate the name of Member State in which clinical investigation is performed, the title of the clinical investigation

[132] **DK, FR**: professional secrets should not be publicly available;

[133] **Pcy:** aspects of transparency and confidentiality are move to Art 53to address them in a systematic manner.

[134] **DS1560/14 AT** add subpoint (h) "*additional data necessary to register a clinical investigation in a public registry which is a primary or partnered registry of, or a data provider to, the WHO ICTRP*" to the list, DK disagrees

[135] **DS 1560/14 AT** add "or the contact person according to Article 50, paragraph 2, subparagraph 2" DK support.

[136] **AT** proposal to add subparagraph (h)

2. Within one week[137] 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.

3. ~~The information ***referred to in paragraph 1*** shall be accessible to the public, through the electronic system referred to in Article 53,~~ [138]~~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.~~

[137] **PT** replace "one week" with "24 hours"; **DK** supports.

[138] **D**K delete paragraph 3, duplicates text in paragraph 1, Article 52

Article 53[139]

Electronic system on clinical investigations

1. The Commission shall, in collaboration with the Member States, set up***,*** ~~and~~ manage ***and maintain*** an electronic system ***portal and data base***[140]

(aa) to create the single identification numbers for clinical investigations ~~referred to in Article 51(1) and to collate and process the following information:~~

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

(ab) to be used as an entry point for the submission of all ~~***applications***~~ ***notifications for clinical investigations referred to in Articles 51(1), 54, 54a, 55 and 58 and for all other submission of data, or processing of data in this context;***

(b) ***for*** the exchange of information ***relating to clinical investigations in accordance with this Regulation*** between the Member States and between them and the Commission ~~in accordance with Article 56~~ ***including those according to Article 51a and 56***[141];

(ba) for information[142] ***by the sponsor in accordance with Article 57;***

~~(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;~~

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[139] **DK** doubts about financial burden of the Electronic system, **DE, IE, ES, FR, HR, AT, PT, UK** agree the provision, **DK, ES** require clarification. **Cion** The DB will be developed as described by the non-paper of the Committee in this regard. The DB will be operational on the date of entry into force of the Regulation. It has been provided a period of 18 months of smooth transition. (Stages of testing, pilot projects, etc.)

4.1 Does your delegation agree to capture also national clinical investigations and related SAE/SA**DE** reporting in the above mentioned electronic system, to be uploaded by Sponsor?				
YES	**NO**	**Neutral**	**Abstention**	**Total**
24	**0**	**2**	**2**	**28**

4.2 Does your Delegation agree to inclu**DE** **also** the information concerning the above mentioned issue in the electronic system?				
YES	**NO**	**Neutral**	**Abstention**	**Total**
25	**0**	**1**	**2**	**28**

[140] **AT** replace "*portal and database*" with **"***system consisting of a portal as the single entry point for the submission of data and information relating to clinical investigations in accordance with this regulation and the data base which shall contain the data and information submitted through the portal,. This system shall be used*".

[141] **DS 1560/14 AT** add "*including those according to Article 51a, and 56*"

[142] **AT** add "*and provision of reports*"

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

(e) for collecting the clinical investigation reports and the summaries thereof for health care professionals and lay persons.

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 [***536***/***2014***] ***as concerns combined***[143] ***clinical investigations of devices with clinical investigations under that regulation***.[144]

[143] **AT** supports narrowing of scope; **Cion** disagrees.
[144] transferred to paragraph 2a for a systematic approach.

2a. [145] ***The information referred to in ~~Art 52~~ paragraph 1 except b ,which shall only be accessible to the Member States and the Commission*** [146], ***shall be accessible to the public, unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:***

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

(b) protection of commercially confidential [147] ***information, especially in the investigators brochure*** [148] [149]***, in particular through taking into account the status of the ~~marketing authorisation~~ conformity assessment for the device, unless there is an overriding public interest in disclosure;***

The information for registration according to Article 52 is not considered confidential [150]***.***

2b ***No personal data of subjects participating in clinical investigations shall be publicly available*** [151].

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145 This paragraph is based on paragraph 3 of Article 52 in the Commission proposal. The changes to that paragraph are as follows:
"The information *referred to in Article 52, paragraph 1,* shall be accessible to the public, unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:
(a) protection of personal data in accordance with Regulation (EC) No 45/2001;
(b) protection of commercially ~~sensitive~~ *confidential* information*, especially in the investigators brochure; in particular through taking into account the status of the conformity assessment for the device, unless there is an overriding public interest in disclosure*;
~~(c) effective supervision of the conduct of the clinical investigation by the Member State(s) concerned.~~
The information for registration according to Article 52 is not considered confidential."
ES doubts about c).

146 **AT** add "*except b ,which shall only be accessible to the Member States and the Commission*"

147 **DK** p3 c) clarify "*commercially sensitive*" **ES** support, **Pcy** specify the term "*sensitive*", harmonise with CTR.

148 **DS 1479/14 AT** usually the document, where sensitive manufacturing or technical information can be found.

149 **DK** delete "*especially in the investigators brochure*", **AT** disagrees.

150 **DS 1479/14 AT** This is publicly available information in open global clinical investigation registries.

151 **Pcy** moved from Article 52.

3. The Commission ~~shall be empowered to~~ ***may*** adopt ~~delegated~~ ***implementing*** acts in accordance with Article 8***8(3)*** determining ~~which other~~ ***how*** information regarding clinical investigations collated and processed in the electronic system shall be publicly accessible ~~to allow~~ ***in view of the*** interoperability with the EU database for clinical trials on medicinal products for human use set up by Regulation (EU) No ~~[~~***536/2014***~~]~~ ***as concerns combined clinical investigations of devices with clinical trials***.[152] Article 53 shall apply.[153]

[152] **AT** replace "*investigation*s" with "*trials*".
[153] **AT, SE** do not support delegated acts.

Article 54[154]

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[155] ~~***and Ethics Committee***~~ 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***[156]***. Article 50 paragraph 5 points (b) to (i),*** ~~Article 50(1) to (3)~~, Article 52, Article 55, Article 56~~(1)~~[157], Article 57~~(1), the first subparagraph of Article 57(2)~~[158]***, Article 59*** [159] 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.

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154 **DS 1482/14 SE, DK, LT** the procedure is not clear; SE does not support notification if the CE-marked device will be used within the intended purpose

155 **IE, UK** delete Ethics Committee. **DE, PT** add Ethics Committee.

156 "it shall be accompanied by the documentation referred to in Chapter II of Annex XIV" excessive request for devices authorised to bear the CE marking- **DS 1488/14 LT** The process is not clear. It is not clear whether such kind of investigation needs approval/authorisation. According to all known ethical guidelines scientific and ethical evaluation is necessary for all clinical investigations in which subjects will experience additional invasive procedures or additional inconveniences. Depending on the scientific and ethical evaluation results approval/authorisation to perform clinical investigation is granted or not granted.

157 **DS 1560/14 AT** delete "(1)"

158 **DS 1560/14 AT** delete "(1) the first subparagraph of Article 57(2)"

159 **DS 1560/14 AT** add "Article 59"

Article 54a[160]

Non substantial modifications to a clinical investigation[161]

The sponsor shall notify immediately[162] ***the Member State(s) ~~and Ethics Committee~~ 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 be 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.***

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[163] impact on the safety, ***health***[164] 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*** the Member State(s) concerned ***~~and the Ethics committee concerned~~***[165] 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***.

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160 **DK, UK** delete Article 54a; **DE,AT, PT** disagree.

161 **DS 1482/14 SE** change title to "*Non-substantial modifications to a clinical investigation*".

162 **HR** clarify timing **DS 1488/14 LT** The text is not clear. Different terminology is used. There are no procedures of "approval" in the proposal. What does it mean "approval OR favourable opinion"? Favourable opinion of Ethic Committee should be mandatory in all cases. The term "application" should be used instead of "notification" as it is stated in Article 51.5.
We would suggest to define the provisions regarding modification to a clinical trial (substantial and non-substantial) in one Article.

163 **DK, PT** should be defined the term "substantial", **DE** distinguish between formal and substantial changes.

164 **DS 1560/14 AT** add "health"

165 **DE, PT** reinstate reference to Ethics Committee, **BE, DK, FR, AT, FI, SE** disagree.

~~2.~~ The sponsor may implement the modifications ~~referred to in paragraph 1~~ at the earliest 30 days after notification, unless the Member State ***~~or Ethics committee~~*** concerned has notified the sponsor of its refusal based on considerations of public health, ~~patient~~ ***subject and user***[166] safety ***or health*** ,~~or~~ ***of*** public policy, ***or issued negative opinion of ethics committee which in accordance with the law of that Member State, is valid for that entire Member State***[167].

Article 56[168]

Corrective measures to be taken by Member States and *information exchange between Member States,*[169]

0a. Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures on its territory:

(a) withdraw or[170] ***revoke the authorisation of a clinical investigation;***

(b) suspend, temporary halt or terminate a clinical investigation;

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

0b. Before the Member State concerned takes any of the measures referred to in paragraph 0a it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion. That opinion shall be delivered within seven days.

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166 **DK** replace "*patient*" with "*subject and user safety or health*".
167 **Pcy** text in accordance with CTR Chapter III.
168 **Pcy** combined Articles 51d and 56 to avoid repetition
169 **DE, IE, AT** requirements for monitoring and inspection should be added.
170 **DS 1560/14 AT** add "*withdraw or*".

1. Where a Member State ***has taken a measure referred to in paragraph 1 or*** 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, ~~***or the concerned Ethics Committee in this Member State has issued a negative opinion***~~[171] [172]***,*** 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.

1a. Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to in paragraph 1.

2. Where a ~~application~~ ***notification*** is withdrawn by the sponsor prior to a decision by a Member State, that ~~Member State shall inform~~ ***information shall be available to***[173] all the other Member States and the Commission ~~of that fact~~, by means of the electronic system referred to in Article 53.

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[171] **DS 1385/14 NL** insert "*or the concerned Ethics Committee in this Member State has issued a negative opinion*" **DS 1488/14 LT** First of all it should be stated that Member States have the right to refuse, suspend, and terminate clinical investigations. Secondly, the reasons/criteria for the refusal, suspension and termination should be defined. Also terminology should be revised and defined. For instance, the translation of "suspension" and "temporary halt" has the same meaning in the Lithuanian language.

[172] **DK** reference to the Ethics Committee should be deleted, **PT** disagrees.

[173] **DE** the information about applications withdrawn by the sponsor prior to a decision by a Member State should not be provided in an active way.

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[174] days , ***in case of safety grounds within 5 days***[175], of the temporary halt ***or early termination, providing a justification***.

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***[176] 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[177]. 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.

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174 **PT, DK** 15 days is a too long period on safety grounds

175 **AT** add "*in case of safety grounds within 5 days*"

176 **DE** in case of early termination clinical investigation report is not feasible, **AT** disagree.

177 **DK** deadline is necessary

3a. A summary of the clinical investigation report for healthcare professionals shall be provided by the sponsor within 1 year following the provision of the clinical investigation report according to paragraph 3. In addition, the sponsor shall provide within the same time frame a summary overview of the clinical investigation report for the general public which is understandable for the lay person.[178]

3b. ***Submission of information and reports according to paragraphs 1 to 4 shall be accomplished through the electronic system referred to in Art. 53. The reports according to paragraphs 3 and 4 shall become publicly accessible through the electronic system, at the latest when the device is CE-marked and before it is placed on the market.***[179]

Article 58

Clinical investigations conducted in more than one Member State[180] [181] [182]

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~~ ***notification*** that, upon receipt, is transmitted electronically to the Member States concerned***, who have voluntarily***[183] ***agreed to that procedure concerning that clinical investigation.***

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[178] **DS 1560/14 AT** add "*A summary of the clinical investigation report for healthcare professionals shall be provided by the sponsor within 1 year following the provision of the clinical investigation report according to para graph 3. In addition, the sponsor shall provide within the same timeframe a summary overview of the clinical investigation report for the general public which is understandable for the lay person*." Support: PT, FR, SE.

[179] **DS 1482/14 SE** add new subparagraph at the end of 57.*3 "All "clinical investigation reports"/ "clinical performance study reports" shall be submitted to the electronic system and become publicly accessible , at the latest when the device is CE-marked and before it is placed on the market*". **AT** support.

[180] **DS 1286/14** Final Report Technical Meeting on Clinical Investigations; 21.5.2014**_UK** suggestion.

[181] **Pcy** noted that this article is very innovative. Art 58 is based on **DS 1479/14 AT** according to the results of the questionnaire. Delegations are invited to submit written comments. WP 10 November discussion of proposal in **Pcy DS 1482/14** and **FR** written suggestion for Coordinated Assessment Procedure.

[182] **DK** procedure is to broad,complicated,resource intensive; **DE, IE, FR, UK** could agree with proposal; **DE** textual corrections are necessary.

[183] **Cion** coordinated procedure should be mandatory (at least for class III medical devices).

2. In the single ~~application~~ ***notification***, 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~~ ***Concerned Member States*** shall ~~agree~~, within six[184] days of ~~submission of~~ the ~~single~~ ~~application~~ ***notification***, ~~with another Member State concerned that the latter shall be~~ ***agree on one of them taking the role of*** the coordinating Member State. ~~If no other Member State accepts to be the~~ ***If they do not agree on a*** coordinating Member State, the ~~Member State~~ ***one*** proposed by the sponsor shall ~~be the coordinating Member State~~ ***take that role***. ~~If another Member State than the one proposed by the sponsor becomes coordinating Member State, the~~ ***The*** deadline***s*** referred to in Article 51~~(2)~~ shall start on the day following the ***notification of the coordinating Member State to the sponsor (notification date)*** ~~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~~ ***notification***, in particular of the documentation submitted in accordance with Chapter II of Annex XIV, except for Sections ***1.13.***[185]; 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[186] of receipt of the single ~~application~~ ***notification*** notify the sponsor ***that it is the coordinating Member State;***

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[184] **DS 1482/14 SE** replace "*six*" with "*ten*"
[185] **AT** add "1.13."
[186] **DS 1479/14 AT** Replace "*6 days" by " ten days".*

(aa)[187] ***within 10 days***[188] ***of the notification date, notify the sponsor***[189] whether the clinical investigation falls within the scope of this Regulation and whether the ~~application~~ ***notification*** is complete, except for the documentation submitted in accordance with Sections ***1.13., 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 ***and notify the sponsor accordingly***. 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~~ ***notification*** is complete, ***having taken into account considerations expressed by the other Member States concerned,*** except for the documentation submitted in accordance with Sections ***1.13., 3.1.3***~~,~~ 4.2, 4.3 and 4.4 of Chapter II of Annex XIV. ***Concerned Member States may communicate to the ~~reporting~~ coordinating***[190] ***Member State any considerations relevant to the validation of the ~~application~~ notification within seven days from the notification date.***[191] Article 51(2) to (4) shall apply to each Member State in relation to the verification that the documentation submitted in accordance with Sections ***1.13. 3.1.3,*** 4.2, 4.3 and 4.4 of Chapter ***II*** of Annex XIV is complete;

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187 In DS 1482/14 called (b).

188 **DS 1482 SE** replace "*10 days*" with "*15 days*"

189 **Pcy** clarification.

190 **DE, SE** replace "*reporting*" with "*coordinating*".

191 **DS 1479/14 AT** 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.*"

(b) establish the results of ~~the coordinated~~ ***its*** assessment in a ***draft assessment*** report to be ***transmitted within [26] days***[192] ***after the validation date to the concerned Member States. Until day [38] after the validation date the other concerned Member States shall transmit their comments and proposals on the draft assessment report and the underlying ~~application~~ notification to the coordinating Member State, which shall take due account of it in the finalization of the final assessment report, to be transmitted within [45] days following the validation date to the sponsor and the concerned Member States. The final assessment report shall be*** taken into account by the other Member States concerned when deciding on the sponsor's ~~application~~notification in accordance with Article 51(5) ***("joint assessment part"), except for Sections 1.13.,3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV("single assessment part"), which shall be assessed separately by each Member State concerned***.[193]

As concerns the assessment of the documentation related to Sections1.13., 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV, done separately by each Member State, the Member State may request, on a single occasion, additional information from the sponsor. The expiry of the deadline pursuant paragraph 2 shall be suspended from the date of the request until such time as the additional information has been received.[194]

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192 **AT** suggests to use CTR timelines, **FR, UK** agree, **SE** timelines should be as long as possible.

193 **DS 1479/14 AT** 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).*"

194 **PT** delete last paragraph.

3a. The Commission may, by means of implementing acts, set out the procedures and timescales for a coordinated assessment led by the coordinating Member State, that shall be taken into account by concerned Member States when deciding on the sponsor's ~~application~~ notification. 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) or in the case of clinical investigations of combination products between medical devices and medicinal products, where the latter are under a concurrent coordinated assessment of a clinical trial[195] under Regulation (EU) 536/2014. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(3).

3b.[196] Each Member State concerned shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. Notification shall be done by way of one single decision within five days from the reporting date. An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

3c.[197] Where the conclusion of the coordinating Member State is that the conduct of the clinical investigation is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State(s)[198] concerned.

Notwithstanding the previous subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State concerning the area of joint assessment only on the following grounds:

(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 national law;

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195 **AT** replace "*investigation* " with "*trial*".
196 Paragraph 4 in DS 1482/14.
197 Paragraph 4a in DS 1482/14.
198 **DS1560/14 AT** replace "*Member State*" with "*Member State (s)*"

(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 3c[199]. 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 concerned[200], and to the sponsor.

3d.[201] A Member State concerned shall refuse to authorise a clinical investigation if it disagrees with the conclusion of the coordinating Member State as regards any of the grounds referred to in the second subparagraph of paragraph 4a, or if it finds, on duly justified grounds, that the aspects addressed in Sections 1.13., 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

3e.[202] Where the conclusion of the coordinating Member State report is that the clinical investigation is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

4. The substantial modifications ***to clinical investigations under Article 58*** ~~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~~ ***~~paragraph 1~~ paragraph 3c***[203] shall be carried out under the direction of the coordinating Member State***, except for substantial modifications concerning sections 1.13., 3.1.3, 4.2, 4.3 and 4.4 of Chapter II of Annex XIV, which shall be assessed by each concerned Member State on its own***.

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199 Reference not correct.
200 **DS1560/14 AT** add "concerned".
201 Paragraph 4b in DS 1482/14.
202 Paragraph 4c in DS 1482/14.
203 **DS 1560/14 AT** replace "paragraph 1" with " paragraph 3c"

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~~ ***administrative*** support to the coordinating Member State in the accomplishment of its tasks provided for in this Chapter.

Article 58a[204]

Review of clinical investigations rules

Five years[205] ***after the date referred to in the first paragraph of Article 97, the Commission shall make a report on the application of Article 58 of the present Regulation and propose a review of the provision of Article 58 in order to ensure a coordinated*** ~~***procedure***~~ ***assessment procedure of clinical investigations conducted in more than one Member State.***

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[206] 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).

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[204] Based on a suggestion from **FR, AT** supports co-decision procedure, **DK** suggests consult Legal Service.

[205] **PT** Replace "*Five years*" with "*four years*".

[206] **DE** delete "*serious*".

2. The sponsor shall report to all Member States where a clinical investigation is conducted without delay[207] any of the following ***by means of the electronic system referred to in Article 53***:

(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[208].

4. In the case of a clinical investigation for which the sponsor has used the single ~~application~~ ***notification*** 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.

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[207] **DK** replace "*without delay*" with "*immediately*"

[208] **AT** combined paragraphs 2 and 3.

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 ***electronic***[209] forms for the ~~application~~ ***notification*** 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 ***electronic*** 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 ***electronic*** 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.

[209] **DE** add "*electronic*".

(g) uniform application of the requirements regarding the clinical evidence/data needed to demonstrate compliance with the general safety and performance requirements specified in Annex I. [210]

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

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[210] **DS1482/14 SE** add to the list "(*g) interpretation regarding the clinical evidence/data which is needed to demonstrate compliance with the essential requirements specified in Annex I".* **AT** agrees.

Definitions to be examied in the meeting of the Working Party on 12 and 13 February 2015.

(15a) 'performance' means ~~any technical characteristics, any effects and any benefit of the device when used for the intended purpose and in accordance with the instructions of use~~ the ability of a medical device to achieve its intended purpose as claimed by the manufacturer;[211]

(15b) 'safety' means ~~reasonable assurance, evaluated upon valid scientific clinical evidence, that a medical device, when used for the intended purpose and in accordance with the instructions of use, provides positive effect on health outweighed the probable risks and is freedom from inacceptable risk~~ the absence of unacceptable ~~clinical~~[212] ***risks, when using the device according to the manufacturer's instructions for use;***[213] [214]

(15c) 'benefit' means the positive effect on health, evaluated upon valid scientific clinical evidence, obtained using a medical device for the intended purpose and in accordance with the instructions of use;[215]

(15d) 'risk' means the combination of the probability of occurrence of harm and the severity of that harm;[216]

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[211] This definition replaces definition (16a) in document 12538/14. As now proposed, the definition is taken from GHTF/SC/N4:2012, Edition 2. **Cion** suggested alignment with GHTF definition.

[212] **ES, PT, Cion** delete "*clinical*".

[213] This definition replaces definition (16b) in document 12538/14. As now proposed, the definition is taken from GHTF/SC/N4:2012, Edition 2. **Cion** suggested alignment with GHTF definition.

[214] **DK**, **PL** object to inclusion of the proposed definition.

[215] This is definition (16c) from document 12538/14. No changes have been done.

[216] This is definition (16d) from document 12538/14. No changes have been done. This definition is from GHTF/SC/N4:2012, Edition 2. **Cion** suggested alignment with GHTF definition.

(15e) 'benefit-risk determination' means the integration of all assessments of benefit and risk of possible relevance for the use of the medical device for the intended purpose, when used in accordance with the instructions of use";[217]

Definitions related to clinical evaluation and clinical investigations[218]:

(32) 'clinical evaluation' means the assessment and analysis[219] of clinical data pertaining to a device in order to verify the safety and performance of the device when used as intended by the manufacturer;[220]

(33) 'clinical investigation' means any systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a device;

(34) 'investigational device' means any device being assessed for safety and/or performance in a clinical investigation;

(35) 'clinical investigation plan' means ~~the~~ ***a*** document~~(s)~~ ***that describes*** ~~setting out~~ the ~~rationale,~~ objectives, design***, methodology, statistical considerations*** and ***organisation*** ~~proposed analysis, methodology, monitoring, conduct and record-keeping~~ of ***a*** ~~the~~ clinical investigation;[221]

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[217] This is definition (16e) from document 12538/14. No changes have been done.

[218] In response to requests by several delegations and Cion during the WP held on 11-12 September 2014, **Pcy** here has, where appropriate, harmonized the definitions with those included in Regulation (EU) No 536/2014 on clinical trials and document GHTF/SC/N4:2012.

[219] **DS 1002/14 DE** replace "*the assessment and the analysis*" with "*a systematic and planned process to continuously generate, collect and analyse*"

[220] ~~**DK, PL** reinstate Cion proposal.~~

[221] ~~**FR** suggests to align with the definition of "*protocol*" in Regulation (EU) No 536/2014. That definition reads:~~
~~" *'Protocol' means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial. The term 'protocol' encompasses successive versions of the protocol and protocol modifications;*"~~

(36) 'clinical data' means the information concerning the safety or performance that is generated from the use of a device and that are sourced from the following:

– clinical investigation(s) of the device concerned,

– clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated,

– ~~published and/or unpublished~~ reports ***published in peer reviewed scientific literature***[222] on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated ~~***published in peer reviewed scientific literature***~~[223];

(37) 'sponsor' means an individual, ~~***legal or physical person,***~~ company, institution or organisation ~~***who***~~ which takes responsibility for ***the*** ~~***setting up of financing***~~, initiation***, for the*** ~~and~~ management ***and for setting up the financing*** of ~~a~~ ***the*** clinical investigation; [224]

(37a) 'subject' means an individual who participates in a clinical investigation either as recipient of an investigational product or as control;[225]

(37b) 'clinical evidence' means the clinical data and clinical evaluation report pertaining to a medical device ~~***of sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety, when used as intended by the manufacturer;***~~[226]

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[222] **DS 1002/14 DE** replace "*published and/or unpublished*" with "*published in peer reviewed scientific literature*"; **DK** do not limit to peer-reviewed scientific literature.

[223] ~~This text, introduced in document 12538/14 has been moved.~~

[224] This definition as here reworded closely follows that that in Regulation (EU) No 536/2014 on clinical trials.

[225] Definition from **DS 1002/14 DE**.

[226] Definition from GHTF/SC/N4:2012.

(37c) 'clinical performance' means the ability of a medical device to achieve its intended purpose as claimed by the manufacturer ~~any direct or indirect medical effects on humans as well as the clinical benefit on patients resulting from the technical or functional, including diagnostic characteristics of a device, when used as intended by the manufacturer~~;[227] [228]

~~(37d) 'clinical benefit' means the positive impact of a device on the health of an individual, to be specified as meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis or a positive impact on patient management or public health, inter alia through the use of diagnostic devices for screening;~~[229] [230]

~~(37e) 'efficacy' means the ability of a medical device to achieve the intended clinical benefit(s) to patients, in the intended target group(s), when the device is used as intended by the manufacturer, under ideal circumstances (as in a pre-market clinical investigation);~~ [231]

~~(37f) 'effectiveness' means the ability of a medical device to achieve the intended clinical benefit(s) to patients, in the intended target group(s), when the device is used as intended by the manufacturer, under normal circumstances of health care practices;~~[232]

(37g) 'equivalence' means the ability of two or more devices, with the same intended purpose, to have similar ~~identical~~[233] *technical characteristics~~,~~ and the same biological and clinical characteristics, when used as intended by their respective manufacturers, to such an extent that there would not be a clinically significant difference in the safety and performance of the devices;*

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227 Definition from GHTF/SC/N4:2012.
228 **IE** delete this definition.
229 Definition from **DS 1002/14 DE**.
230 Definition deleted following a suggestion from **UK**.
231 Definition deleted following a suggestion from **UK**.
232 Definition deleted following a suggestion from **UK**.
233 **ES, NL, Cion** against "*identical*"; **PT** suggests to consider similar technical characteristics and the same biological and clinical characteristics, following MEDDEV.

(37h) 'investigator' means an individual responsible for the conduct of a ~~to perform critical clinical investigation related procedures or to make important~~ clinical investigation-~~related decisions~~ at a clinical investigation site;[234] [235]

(37i) 'principal investigator' means an investigator who is the responsible leader of a ~~leads an investigation~~ team of investigators at ~~an~~ a clinical investigation site;[236] [237] [238]

(37j) 'coordinating investigator' is an investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation;[239] [240] [241]

(37k) 'informed consent' means ~~a statement by which~~ a subject's free and voluntar~~ily~~ ~~confirms~~ expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation 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 the clinical investigation;[242] [243] [244]

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234 The corresponding definition in Regulation (EU) No 536/2014 (on clinical trials) reads: "*'Investigator' means an individual responsible for the conduct of a clinical trial at a clinical trial site;*".

235 Original definition in 12538/14 from **DS 1002/14 DE**.

236 The corresponding definition in Regulation (EU) No 536/2014 (on clinical trials) reads: "*'Principal investigator' means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site;*".

237 Original definition in 12538/14 from **DS 1002/14 DE**.

238 **NL, UK** delete this definition.

239 There is no corresponding definition in Regulation (EU) No 536/2014 (on clinical trials).

240 Definition from **DS 1002/14 DE**.

241 **NL, UK** delete this definition.

242 Original definition from **DS 1002/14 DE**.

243 The corresponding definition in Regulation (EU) No 536/2014 (on clinical trials) reads: "*'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 the clinical trial;*".

244 **NL** delete this definition.

(37l) 'Ethics committee' means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations;[245]

(38) 'adverse event' means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device;

(39) 'serious adverse event' means any adverse event that led to any of the following:

- death,
- serious deterioration in the health of the subject, that resulted in any of the following:
  - (i) life-threatening illness or injury,
  - (ii) permanent impairment of a body structure or a body function,
  - (iii) hospitalisation or extending the duration of hospitalisation,
  - (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- foetal distress, foetal death or a congenital abnormality or birth defect;

(40) 'device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer;

_____

[245] Definition from Regulation (EU) No 536/2014 (on clinical trials).

ANNEX XIII

CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

PART A: CLINICAL EVALUATION[246]

1. To ***plan, continuously*** conduct ***and document*** a clinical evaluation, a manufacturer shall:

   a) establish and update a clinical evaluation plan, which ~~should~~ shall include at least:

   - ***an*** ~~identify~~ ***identification of*** the general safety and performance requirements that require support from relevant clinical data;
   - ***a specification of the intended ~~use(s)~~ purpose[247] of the device;***
   - ***a~~n~~ clear indication of specified target groups with clear[248] indications and contraindications;***
   - ***a detailed description of intended clinical benefits to patients with ~~meaningful~~ relevant[249] and specified clinical outcome parameters;***
   - ***a specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side effects;***
   - ***an indication and specification of parameters to be used to determine the acceptability of the benefit risk ratio for the various indications and intended purpose(s) of the device according to the state of the art in medicine;***

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[246] **IE Pcy** : Experts suggested that certain definitions such as "clinical benefit", "clinical performance", "clinical evidence", "effectiveness" and possibly "efficacy" should be developed and included in Chapter 2. **DK** reserves the right of a closer examination of the entire text.**FR** in general agrees with the content of the Annexes, provide coherence with Chapter VI.

[247] **Cion** replace and harmonize "*use* " with "*purpose*" "

[248] **AT** delete "*clear*".

[249] **SE** replace "*meaningful*" with "*relevant*"; **Cion** "*meaningful*" is subjective.

- ***an indication how risk/benefit issues relating to specific components (e.g. use of pharmaceutical, non-viable animal/human tissues) are to be addressed;***
- ***a clinical development plan indicating progression from exploratory (e.g. first-in-man studies, feasibility, pilot studies) to confirmatory investigations (e.g. pivotal clinical investigations)[250] and PMCF [251] according to Part B of this Annex with an indication of milestones and a description of potential acceptance criteria[252];***

b) identify available clinical data relevant to the device and its intended ~~use~~***(s) purpose and eventual gaps in clinical evidence*** ~~generated~~ through ***a systematic*** scientific literature search~~, clinical experience and/or clinical investigations~~;

c) appraise the clinical data sets by evaluating their suitability for establishing the safety and performance of the device;

d) generate any new or additional clinical data needed to address outstanding issues ***by properly designed clinical investigations in accordance with the clinical development plan***;

e) analyse all relevant clinical data to reach conclusions about the safety and ***clinical*** performance ***(including clinical benefits)*** of the device.

~~2. 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.~~[253]

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[250] **DE** regulation of exploratory investigations is not appropriate under this Proposal. **UK** non-commercial exploratory clinical investigations and that these should be left to national ethics committee review.

[251] **AT** add "*appropriately aligned with the PMCF plan*".

[252] **UK** replace with *'a clinical development plan indicating progression from exploratory (e.g. first-in-man studies, feasibility, pilot studies) to confirmatory investigations (e.g. pivotal clinical investigations)[252] and should be appropriately aligned with the PMCF plan according to Part B of this Annex with an indication of milestones and a description of potential acceptance criteria;*.

[253] **IE Pcy** Delete and relocate to Article 49(1) (MDEV-21).

3. The clinical evaluation shall be thorough and objective, considering both favourable and unfavourable data. Its depth and extent shall be proportionate and appropriate to the nature, classification, intended ~~use~~***~~(s)~~ purpose***, manufacturer's claims and risks of the device in question.

~~4. Clinical data relating to another device may ***only*** be relevant where equivalence is demonstrated of the device subject to clinical evaluation to the device to which the data relates. Equivalence can only be demonstrated when the device that is subject to clinical evaluation and the device to which the existing clinical data relates have the same intended purpose ***and user*** and when the technical and biological characteristics of the devices and the medical procedures, ***the clinical environment and, mode of application*** are similar to such an extent that there would ***not*** be a clinically significant difference in the safety and performance of the devices. ***Considerations of equivalence must always be based on proper scientific justification***.~~ [254]

4a. [255] ***A clinical evaluation can only be based on clinical data of a similar device for which equivalence to the device in question can be demonstrated. Technical, biological and clinical characteristics shall be taken into consideration for the demonstration of equivalence:***

- ***Technical: be of similar design; used under similar conditions of use; have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms); use similar deployment methods (if relevant); have similar principles of operation and critical performance requirements.***
- ***Biological: Use same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables.***

[254] **Pcy** deleted because overlap with paragraph 4a.
[255] **IE Pcy** text based on MEDDEV 2.7.1. **UK** agrees.

- ***Clinical: Used for the same clinical condition or purpose (including similar severity and stage of disease), at the same site in the body, in a similar population (including age, anatomy, physiology); have same kind of user,[256] have similar relevant critical performance according to the expected clinical effect for a specific intended ~~use(s)~~ purpose.***

These characteristics shall be similar to such an extent that there would be no clinically significant difference in the clinical performance and safety of the device. Considerations of equivalence must always be based on proper scientific justification[257].

~~5. In the case of implantable devices and devices falling within class III, clinical investigations shall be performed *except in very specifically defined and duly justified circumstances where there is a sufficient level of scientifically valid data from previous clinical investigations to address each of the relevant general safety and performance requirements and required specifications and that it can be clearly demonstrated that patient safety will not be improved by performing a clinical investigation. Specific permissible exceptions to this rule will be defined in guidance.*~~ [258] ~~unless it is duly justified to rely on existing clinical data alone. Demonstration of equivalence in accordance with Section 4 shall generally not be considered as sufficient justification within the meaning of the first sentence of this paragraph.~~[259]

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256 **AT** add "*have same kind of user*"

257 **Pcy** moved from the deleted paragraph 4.

258 **FR, UK** delete paragraph 5 redundant as doubles paragraph 2a of Article 49, **DE, PT** disagree, **Cion** suggests to avoid reference to guidance documents if we refer to exceptions.

259 **DE, FR, NL, PT** delete. **DK, UK** important to ensure that iterative development is permitted and that clinical investigations were not performed when there was adequate existing data and no improvement in patient safety as a result of performing the investigation. **DK** refer to the concept of equivalence in Chapter VI. **Cion** in favour of this suggestion.

6. The results of the clinical evaluation and the clinical ~~data~~[260] ***evidence*** on which it is based shall be documented in the clinical evaluation report which shall support the assessment of the conformity of the device.

The clinical ~~data~~ ***evidence*** together with non-clinical data generated from non-clinical testing methods and other relevant documentation shall allow the manufacturer to demonstrate conformity with the general safety and performance requirements and shall be part of the technical documentation of the device in question.

PART B: POST-MARKET CLINICAL FOLLOW-UP

1. Post-market clinical follow-up, hereinafter: PMCF, is a continuous process to update the clinical evaluation referred to in Article 49 and Part A of this Annex and shall be part of the manufacturer's post-market surveillance plan. To this end, the manufacturer shall proactively collect and evaluate clinical data from the use in or on humans of a device which ~~is authorised to~~ bear***s*** the CE marking, ***placed on the market or put into service within*** its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, the continued acceptability of identified risks and to detect emerging risks on the basis of factual evidence.

2. The PMCF shall be performed pursuant to a documented method laid down in a PMCF plan.

2.1. The PMCF plan shall specify the methods and procedures to proactively collect and evaluate clinical data with the aim of

(a) confirming the safety and performance of the device throughout its expected lifetime,

(b) identifying previously unknown side-effects and monitoring the identified side-effects and contra-indications,

(c) identifying and analysing emergent risks on the basis of factual evidence,

[260] **DK** reinstate "*data*".

(d) assuring the continued acceptability of the benefit/risk ratio referred to in Sections 1 and 5 of Annex I, and

(e) identifying possible systematic misuse or off-label use of the device with a view to verify the correctness of its intended purpose.

2.2. The PMCF plan shall ***include at least:*** ~~lay down, in particular~~

(a) the general methods and procedures of the PMCF to be applied, such as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data;

(b) the specific methods and procedures of PMCF to be applied ***such as***[261] evaluation of suitable registers or PMCF studies;

(c) a rationale for the appropriateness of the methods and procedures referred to in points (a) and (b);

(d) a reference to the relevant parts of the clinical evaluation report referred to in Section 6 of Part A of this Annex and to the risk management referred to in Section 2 of Annex I;

(e) the specific objectives to be addressed by the PMCF;

(f) an evaluation of the clinical data related to equivalent or similar devices,

(g) reference to relevant ***Common Specifications***, standards and guidance on PMCF ~~[CTS]~~.

(h) a detailed and adequately justified time schedule for PMCF activities (e.g. analysis of PMCF data and reporting) to be undertaken by the manufacturer.

3. The manufacturer shall analyse the findings of the PMCF and document the results in a PMCF evaluation report that shall be part of the ***clinical evaluation report and the***[262] technical documentation.

4. The conclusions of the PMCF evaluation report shall be taken into account for the clinical evaluation referred to in Article 49 and Part A of this Annex and in the risk management referred to in Section 2 of Annex I. If through the PMCF the need for ***preventive and/or*** corrective measures has been identified, the manufacturer shall implement them.

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[261] **AT** add "*such as*".

[262] **AT** add "*clinical evaluation report and the*".

ANNEX XIV

CLINICAL INVESTIGATIONS

I. General requirements

1. Ethical considerations[263]

Every step in the clinical investigation, from first consideration of the need and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles~~, as for example those laid down in the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in 1964, and last amended by the 59th World Medical Association General Assembly in Seoul, Korea, in 2008~~[264] [265] [266] [267].

[263] **UK** any wording on ethics committees clearly must respect national competence. **UK** considers it will be useful to reflect what is agreed on the clinical trials regulation.

[264] It had also been suggested to add a reference "*and by the 64th World Medical Association General Assembly in Fortaleza, Brazil, in 2013"*.

[265] To avoid extensive discussions, the **Pcy** proposes to align with CTR by adding a recital: '*This Regulation is in line with the major international guidance documents on clinical trials, such as the 2013 version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki'*

[266] **FR** Add '*This Regulation is in line with the major international guidance documents on clinical trials, such as the most recent (2008) version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki'* (Recital 63 Clinical Trials Proposal). **DE** in favour of a reference to general ethical principles. **Cion** in favour of using text from Recital 63 of the Clinical Trials Proposal.

[267] **FR, AT, PT, SE** reference to Declaration of Helsinki should be kept; replace "*as for example*" with "*consistent with*", delete "*on Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in 1964, and last amended by the 59th World Medical Association General Assembly in Seoul, Korea, in 2008*", **DE, Cion** Declaration of Helsinki should not be legally binding, **ES** suggests to add reference to the Declaration of Helsinki in recitals; **BE** supports **DE, ES, Cion**.

2. Methods

2.1. Clinical investigations shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device as well as the safety, performance and benefit/risk related aspects referred to in Article 50(1); these investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions. ***The rationale for the design and chosen statistical methodology shall be presented as further described in Section 3.6 of this Annex.***

2.2. The ~~***clinical***~~[268] procedures used to perform the investigations shall be appropriate to the device under ~~examination~~ ***investigation***.

2.2a. The research methodologies used to perform the investigation shall be appropriate to the device under investigation.

2.3. Clinical investigations shall be performed ***according to the evaluation plan by a sufficient number of intended users***[269] ***and*** in ***a clinical environment that are representative of the intended normal conditions of*** circumstances ~~similar to the normal conditions~~ of use of the device ***in the target patient population***. ***These shall be in line with the Clinical Evaluation Plan as referred to in Part A of Annex XIII.***

2.4. All the appropriate ***technical and functional*** features ***of the device***, ~~including~~ ***in particular*** those involving the safety and performance~~s of the device~~, and ~~its~~ ***their*** effect on ~~patients~~ ***subject outcome*** shall be ***appropriately addressed and*** examined ***by the investigational design***. ***A list of the technical and functional features of the device and related subject outcomes shall be provided.***

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[268] **DK** delete term "*clinical*", restrictive.

[269] **DK** number of users can be small in specific clinical investigations; **AT** suggests adding "*according to the evaluation plan*".

2.4a. The endpoints of the Clinical Investigation shall address the intended purpose, clinical benefits, performance[270] and safety of the device. The endpoints shall be determined and assessed using scientifically valid methodologies. The primary endpoint shall be appropriate to the device and clinically relevant.

~~2.5. The investigations shall be performed under the responsibility of a medical practitioner or another authorised qualified person~~ ***, authorised by national law,*** ~~in an appropriate environment.~~ ~~***The medical practitioner or other authorised person shall have the necessary professional experience and training in the relevant medical field and in clinical research methodology.***~~[271]~~

2.6. The medical practitioner or other authorised person shall have access to the technical and clinical data regarding the device. ***Personnel involved in the conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational device, the clinical investigation plan and good clinical practice. This training shall be verified and where necessary arranged by the sponsor and documented appropriately.***

2.7. The clinical investigation report, signed by the medical practitioner or other authorised person responsible, shall contain a critical evaluation of all the data collected during the clinical investigation, including negative findings.

II. Documentation regarding the ~~application~~ *notification* for clinical investigation

For investigational devices covered by Article 50 the sponsor shall draw up and submit the ~~application~~ ***notification*** in accordance with Article 51 accompanied by the ***following documents*** ~~documentation~~ as ***set out*** ~~laid down~~ below:

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[270] **DK** add "*performance*".

[271] "*in the relevant medical field and in clinical research methodology"* moved to Article 50(8), and the rest is deleted to avoid repetition.

1. ~~Application~~ *notification* form

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

1.1. Name, address and contact details of the sponsor and, if applicable, name, address and contact details of his contact person ***or legal representative according to Article 50(2)*** established in the Union.

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

1.3. Title of the clinical investigation.

1.4. Single identification number in accordance with Article 51(1)[272].

1.5. Status of the clinical investigation ***~~application~~ notification*** (~~e.g.~~ ***i.e.*** first submission, resubmission, significant amendment).

1.5a. Details/reference to the Clinical Evaluation Plan (e.g. including details of the design phase of the clinical investigation).

1.6. If resubmission with regard to same device, previous date(s) and reference number(s) of earlier submission(s) or in the case of significant amendment, reference to the original submission. ***The sponsor shall identify all of the changes from the previous submission together with a rationale for those changes, in particular, whether any changes have been made to address outcomes of previous Competent Authority or Ethics Committee reviews.***

1.7. If parallel submission for a clinical trial on a medicinal product in accordance with Regulation (EU) No ~~[…~~***536/2014***~~…]~~ [on clinical trials on medicinal products for human use], reference to the official registration number of the clinical trial.

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[272] **Pcy** subject to revision to ensure accordance with new numbering.

1.8. Identification of the Member States, EFTA countries, Turkey and third countries in which the clinical investigation shall be conducted as part of a multicentre/multinational study at the time of ~~application~~ ***notification***.

1.9. Brief description of the investigational device***, its classification and other information necessary for the identification of the device and device type*** ~~(e.g. name, GMDN code or internationally recognised nomenclature code, intended purpose, risk class and applicable classification rule according to Annex VII)~~.

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

1.11. Summary of the clinical investigation plan (objective(s) of the clinical investigation, number and gender of subjects, criteria for subject selection, subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation).

1.12. If applicable, information regarding a comparator device***, its classification and other information necessary for the identification of the comparator device.*** ~~***(e.g. identification of the comparator device or medicinal product).***~~

1.13. Evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the Clinical Investigation Plan.

1.14. Details of the anticipated start date and duration of the investigation.

1.15. Details to identify the notified body, if the sponsor is using one at the point of ~~***application***~~ ***notification for clinical investigation.***

1.16. Confirmation that the sponsor ~~gives permission for~~[273] is aware that the competent authority may ~~to~~ contact the ethics committee assessing the ~~application~~ notification.

1.17. The statement referred to in section 4.1 of this Annex.

2. Investigator's Brochure

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

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

2.2. Manufacturer's instructions for installation, ***maintenance, ~~cleaning~~ maintaining hygiene standards***[274] and use, including storage and handling requirements, as well as the label and instructions for use to the extent that this information is available. ***In addition, information relating to any relevant training required.***

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

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[273] **FR** Asks clarification on p 1.17. **IE** "This text was added following a discussion with the experts. Some AC have experienced reluctance of the sponsor. If required the AC can ask for opinions of ethics committees. Some Member States had experienced problems in terms of privacy.
Wording "*permission*" is not suitable. **AT** support **BE** we could use "*informed*" .:"*Has been Informed*".

[274] **AT** replace "*cleaning*" with "*maintaining hygiene standards*".

2.4. Existing clinical data, in particular

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

2.5. Summary of the risk/benefit analysis and the risk management, including information regarding known or foreseeable risks, any undesirable effects, contra-indications and warnings.

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

2.7. ~~Reference to harmonised or other internationally recognised~~ ***A list detailing the fulfilment of the*** ~~***essential***~~ ***relevant general safety and performance requirements***[275] ***set out in Annex I, including the*** standards ***and Common*** ~~***Technical***~~ ***Specifications applied,*** ~~complied with~~ in full or in part***, as well as a description of the solutions for fulfilling the*** ~~***essential***~~ ***relevant general safety and performance requirements***[276]***, in so far as these standards and C***~~***T***~~***TS have not or only been partly fulfilled or are lacking***.

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[275] AT replace "*essential requirements*" with "*relevant general safety and performance requirements*".

[276] AT replace "*essential requirements*" with "*relevant general safety and performance requirements*".

2.7a. A detailed description as applicable of the clinical procedures and diagnostic tests used in the course of the clinical investigation and in particular information on any deviation from normal clinical practice.

~~2.8. A clause that any updates to the IB or any other relevant information that is newly available shall be brought to the attention of the investigators.~~

3. Clinical Investigation Plan

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

3.1. General

3.1.1. Identification of the clinical investigation and the CIP.

3.1.2. Identification of the sponsor – ***name, address and contact details of the sponsor and, if applicable, the name, address and contact details of his contact person/legal representative according to Article 50(2)***[277] ***established in the Union***.

3.1.3. Information on the principal investigator ***at each investigational site, the coordinating investigator for the investigation, the address details for each investigation site and the emergency contact details for the principal investigator at each site*** ~~including their qualifications, and on the investigation site(s)~~. ***The roles, responsibilities and qualifications of the various kinds of investigators have to be specified in the Clinical Investigation Plan.***

3.1.4. Overall synopsis of the clinical investigation.

[277] AT add "*according to Article 50(2)*".

3.2. Identification and description of the device, including its intended purpose, its manufacturer, its traceability, the target population, materials coming into contact with the human body, the medical or surgical procedures involved in its use and the necessary training and experience for its use***, background literature search, the current state of the art in clinical care in the relevant field of application and the proposed benefits of the new device***[278].

~~3.3. Justification for the design of the clinical investigation.~~

3.4. Risks and ***clinical*** benefits of the device ~~and~~ ***to be examined, with justification of the corresponding specific clinical outcomes being used.***
Description of the relevance of the clinical investigation ***in the context of the state of the art of clinical practice***.[279]

3.5. Objectives and hypotheses of the clinical investigation.

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

3.6.1. General information such as type ***and phase*** of investigation with rationale for choice, endpoints, variables ***according to clinical evaluation plan***.

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

3.6.3. Information on subjects, ***selection criteria,*** ~~including~~ size of investigation population***, representativity of investigation population to target population*** and, if applicable, information on vulnerable ~~populations~~ ***subjects involved (e.g. children, immuno-compromised, elderly, pregnant women)***.

3.6.3a. Details of measures to be taken to minimise bias (e.g. randomisation) and management of potential confounding factors.

[278] **DK** delete subparagraph 3.2.
[279] **DK** delete "*state of the art*"; **BE, FR, AT, Cion** disagree.

3.6.4. Description of the ***clinical*** procedures ***and diagnostic methods*** related to the clinical investigation ***and in particular highlighting any deviation from normal clinical practice***.

3.6.5. Monitoring plan.

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

3.8. Data management.

3.9. Information about any amendments to the CIP.

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

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

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

3.13. ***Description of the*** Informed consent process.

3.14. Safety reporting, including definitions of adverse events and serious adverse events***, device deficiencies***[280], procedures and timelines for reporting.

[280] **AT** add "*device deficiencies*,".

3.15. Criteria and procedures for ***follow up of subjects following completion of an investigation, procedures for follow up of subjects in the case of*** suspension or early termination~~ of the clinical investigation~~ ***procedures for follow up of subjects who have withdrawn their consent and procedures for subjects lost to follow up***.

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

3.16a. List of the technical and functional features of the medical device indicating those that are covered by the investigation.

3.17. Bibliography.

4. Other information

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

~~This statement may be supported by an attestation issued by a notified body.~~

4.2. Where applicable according to national law, copy of the opinion(s) of the ethics committee(s) concerned as soon as available.

4.3. Proof of insurance cover or indemnification of subjects in case of injury, according to ***Article 50d and*** the ***corresponding***[281] national law.

[281] **AT** add "*Article 50.d and the corresponding*", replace "*law*" with "*legislation*".

4.4. Documents ~~and procedures~~[282] to be used to obtain informed consent***, including the patient information sheet and the informed consent document***.

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

- organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;
- a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects concerned in clinical investigations;
- a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

4.6. Full details of the available technical documentation, for example detailed risk analysis/management documentation or specific test reports ~~should~~ shall[283] ***be submitted to the Competent Authority reviewing an ~~application~~ notification upon request.***[284]

III. Other sponsor's obligations

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

2. ***The Sponsor shall have an agreement in place to ensure that the serious adverse events are reported by the Investigator(s) to the Sponsor in a timely manner*** ~~The reportable events shall be provided by the investigator(s) in timely conditions~~.

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[282] **AT** reinstate "*and procedures*".
[283] **DK** replace "*should*" with "*shall*".
[284] **IT** important to ensure that detailed technical documentation was made available for a detailed review if required by the National Competent Authority.

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

Each Member State shall make provision that this documentation is kept at the disposal of the competent authorities for the period indicated in the first sentence of the preceding paragraph in case the sponsor, or his contact person, established within its territory goes bankrupt or ceases its activity prior to the end of this period.

4. The Sponsor shall appoint a monitor that is independent from the investigation site to ensure that the investigation is conducted in accordance with the Clinical Investigation Plan, the principles of Good Clinical Practice and this Regulation.

5. The Sponsor is obliged to complete follow up of investigation subjects.

6. The Sponsor shall provide evidence to assure that the investigation is being conducted in line with Good Clinical Practice, for instance through internal or external inspection.

7. The Sponsor shall prepare a clinical investigation report which shall include at least the following, as set out below:

- ***Cover/introductory page(s) indicating the title of the investigation, the investigational device, the single identification number, the CIP number and the details with signatures of the coordinating investigators and the principal investigators from each investigational site. Details of the author and date of the report.***
- ***A summary of the investigation should include the title, purpose of the investigation, description of the investigation, investigational design and methods used, the results of the investigation and conclusion of the investigation. The completion date of the investigation, and in particular details of early termination, halts or suspensions of investigations.***
- ***Investigational device description, in particular clearly defined intended ~~use~~ purpose.***

- ***Clinical investigation plan summary – objectives, design, ethical aspects, monitoring and quality measures, selection criteria, target patient populations, sample size, treatment schedules, follow up duration, concomitant treatments, statistical plan (hypothesis/sample size calculation, analysis methods) and justification.***
- ***Results of the clinical investigation – subject demographics, analysis of results ~~with application~~ related to chosen[285] endpoints, details of subgroup analysis (with rationale and justification), compliance to CIP, follow up of missing data and patients withdrawing/lost to follow up from investigation.***
- ***Summary of serious adverse events, adverse device effects and device deficiencies and any relevant corrective actions.***
- ***Discussion/Overall conclusions – safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device, limitations of the investigation.***

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[285] **AT** replace "*with application*" by "*related to chosen*".