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Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation

This document aims to explain the interplay between the Clinical trials Regulation (EU) 536/2014[1] and the General data protection Regulation (EU) 2016/679[2], hereinafter the GDPR.

It will be relevant only when the clinical trials Regulation becomes applicable except for question 11 which explains the current situation under the Clinical Trials Directive[3].

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This guideline reflects the state of play after the consultation of the European Data protection Board[4].

Please note that it is the data protection authorities (DPA`s) of the Member States who are competent for monitoring and enforcing the application of GDPR.[5] They are the natural interlocutors and first point of contact for the public, businesses and public administrations for questions regarding the GDPR. The data protection authorities' role includes informing controllers and processors of their obligations and raising the general public's awareness and understanding of the risks, rules, safeguards and rights in relation to data processing.

Generally speaking, the main contact point for questions on data protection is the DPA in the EU Member State where the company/organisation is based. However, if the company/organisation processes personal data in different EU Member States or is part of a

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1.
[2] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC, *OJ L 119, 4.5.2016, p. 1.*
[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p. 34.
[4] Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the GDPR
[5] To find the national data protection authorities please see https://edpb.europa.eu/about-edpb/board/members_en

group of companies established in different EU Member States, that main contact point may be a DPA in another EU Member State. In the case of cross-border processing of personal data: see Article 29 Working party Guidelines for identifying a controller or processor's lead supervisory authority.[6] This section should be read together with the question and answer documents on the General Data protection Regulation (EU) 2016/679.[7]

Q1. What are the general obligations of the Clinical Trials Regulation with regard to personal data?

The purpose of a clinical trial is to gather reliable and robust data on an investigational medicinal product. This fundamental principle is confirmed by Article 3(b) of the Clinical trials Regulation (CTR).

From this basic principle stems the obligation on the sponsor/investigator to follow the approved protocol and the good clinical practice principles (Article 47 of CTR).

Additionally the CTR strengthens certain measures requiring the sponsor/investigator to record, process, store and handle data in such a way that it can be accurately reported, interpreted and verified, while preserving the confidentiality of the records and requiring appropriate technical and organisational measures to protect information and personal data (Article 56 of CTR).

In addition to that, the sponsor is legally obliged by the CTR to carry out a range of activities (including those detailed in chapter VIII of the CTR) for instance:

- report the results of that trial (Article 37(4) and (8) of CTR);
- perform the safety reporting (Articles 41-43 of CTR); and
- archive the clinical trials master file for 25 years and the medical files of subjects for the time period as prescribed by national law (Article 58 of the CTR)[8].

The sponsor is subject to Member States inspections (Article 78 of CTR) in the context of which Member States' GCP[9] inspectors are entitled to have access to clinical trial data (Article 24 of Directive 2005/28/EC and Article 10(2) of Commission Implementing Regulation (EU) 2017/556) and in the latter Regulation, also the individual patient records.

The clinical trial protocol, authorised under the CTR, defines the purposes and conditions for which the data of clinical trial subjects will be processed. Subjects should be properly informed on the processing of his/her personal data (see Q5).

[7] https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en.
[7] https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en.
[8] As regards the data of a clinical trial that will be used to support the marketing authorisation application, the retention period pursuant to the CTR takes precedence over the obligations in Annex I of Directive 2001/83/EC. Thus, compliance with the requirements of Article 58 of the CTR is required also when using the data of the clinical trial to support the Marketing authorisation applications as regards the data retention periods.
[9] GCP: Good clinical practices.

In addition to this, it must be noticed that Article 93 of the CTR provides that "*Member States shall apply Directive 95/46/EC [now repealed by the GDPR] to the processing of personal data carried out in the Member States pursuant to this Regulation" and that "Regulation (EC) No 45/2001 [repealed by Regulation 2018/1725] shall apply to the processing of personal data carried out by the Commission and the Agency pursuant to this Regulation*". The GDPR as well makes express references to the relevant legislation applicable to clinical trials[10]. It follows that both legislations apply simultaneously...

Q2. Who is responsible for determining the correct legal basis for personal data processing in the context of clinical trial?

According to the principle of accountability, it is the obligation of the data controller (sponsor/clinic-institution of the investigator) to implement the appropriate technical and organisational measures to ensure and be able to demonstrate that the personal data are processed in accordance with the data protection rules (Article 24 of GDPR). The controller must ensure compliance of the processing operations carried out in the context of a clinical trial with all the data protection rules in GDPR (including ensuring respect of the data protection principles, providing information on the processing to data subjects, appointing a Data Protection Officer where required, maintaining records of processing activities, facilitating the exercise of individuals' rights, etc.). It stems from above, that the controller (sponsor/clinic-institution of the investigator) is responsible to determine the legal basis for processing of personal data.

In case of questions please consult the data protection authorities (DPA`s) established in the Member States[11]. Regarding cross-border processing by one data controller a lead DPA will coordinate the cooperation of all the DPAs concerned in order to ensure consistency (Article 56 of the GDPR).[12] Regarding multiple investigators, DPAs will need to cooperate.

Q3. What is the legal basis for processing of personal data of clinical trial subjects in the context of clinical trials (primary use) carried out in accordance with the Clinical Trial Regulation?

All processing operations related to a specific clinical trial protocol during its whole lifecycle, from the starting of the trial to deletion at the end of the archiving period including data in marketing authorisation, shall be understood as primary use of clinical trial data. Not all processing operations relating to such "primary use" of clinical trial data pursue the same purposes and fall within the same legal basis.

The overall objective of the CTR is to achieve a harmonised internal market as regards clinical trials and medicinal products for human use, taking as a starting point a high level of

[10] Recital 156 and recital 161 of the GDPR.
[11] http://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=612080.
[12] See Article 29 Working party Guidelines for identifying a controller or processor's lead supervisory authority http://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=611235.

protection of health, while setting high standards of quality and safety for medicinal products by ensuring that data generated in clinical trials are reliable and robust[13].

The overall objective of the GDPR is to protect fundamental rights and freedoms of natural persons and in particular their right to the protection of personal data. For transparency reason, protection of personal data should be at the centre of the data controllers 'decision.

In particular, processing operations purely related to research activities must be distinguished from processing operations related to the purposes of protection of health, while setting standards of quality and safety for medicinal products by generating reliable and robust data (reliability and safety related purposes); these two main categories of processing activities fall under different legal bases.

1. Processing operations related to reliability and safety purposes

The processing operations which are necessary for compliance with a legal obligation to which the controller is subject may be justified under Article 6(1) (c) of the GDPR. The legal obligations to which the sponsor and/or the investigator are subject to may be expressly provided by the CTR and by relevant Union and national provisions.

This is notably the case, for instance, for obligations relating to the performance of **safety reporting** under Articles 41 to 43 of the CTR, and obligations concerning the **archiving** of the clinical trial master file (25 years according to Article 58 CTR) and the medical files of subjects (which is to be determined by national law according to the same provision). The same applies to any disclosure of clinical trial data to the national competent authorities in the course of an **inspection** in accordance with relevant national rules (see Article 78 CTR).

The corresponding appropriate condition for lawful processing of special categories of data in the context of these obligations shall be **Article 9(2)(i)**: "*processing is* n*ecessary for reasons of public interest in the area of public health, such as [...] ensuring high standards of quality and safety of health care and of medicinal products or medical devices, on the basis of Union or member State law, which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular professional secrecy*".

2. Processing operations purely related to research activities[14]

Processing operations purely related to research activities in the context of a clinical trial cannot, however, be derived from a legal obligation. According to the European Data protection board (EDPB, the processing of personal data is lawful and falls under one of the three legal bases, depending on the whole circumstances attached to a specific clinical trial:

[13] Recital 82 CTR and Article 3(b) CTR.

[14] Article 29 Working Party Guidelines on consent under Regulation 2016/679 of 10 April 2018, p. 27 states that the notion of scientific research may not be stretched beyond its common meaning and understand that 'scientific research' in this context means a research project set up in accordance with relevant sector-related methodological and ethical standards, in conformity with good practice.

- a task carried out in the **public interest** under **Article 6(1) (e)** in conjunction with **Article 9(2), (i) or (j)** of the GDPR; or
- the **legitimate interests** of the controller under **Article 6(1) (f)** in conjunction with **Article 9(2) (j)** of the GDPR; or
- under specific circumstances, when all conditions are met, data subject's **explicit consent** under **Article 6(1) (a)** and **9(2) (a)** of the GDPR.

2.1 Public interest

Article 6 (1) (e) allows processing of personal data where such processing is necessary for the performance of a task carried out in the public interest, on the basis of an EU or national law. The Clinical Trials Regulation defines by law certain processing activities, which are necessary for the performance of a task carried out in the public interest for purposes outlined in the approved clinical trial protocol, in this case to pursue the general public interest of the Union in safeguarding public health. Therefore, in such cases EU law provides the legal basis for the processing of personal data gathered in the context of clinical trials. The processing of personal data in the context of clinical trials can thus be considered as necessary for the performance of a task carried out in the public interest when the conduct of clinical trials directly falls within the mandate, missions and tasks vested in a public or private body by Union or national law.

The legal basis identified under Article 6 shall be supplemented with the condition for processing special categories of data under Article 9 of the GDPR. Depending on the specific circumstances of a clinical trial and on the legal basis used as described above, the appropriate Article 9 condition for all processing operations of sensitive data for purely research purposes could be "reasons of public interest in the area of public health [...] on the basis of Union or Member State law" (Article 9(2)(i)), or "scientific ... purposes in accordance with Article 89(1) based on Union or Member State law"(Article 9(2)(j)).

2.2 Legitimate interest

For other situations where the conduct of clinical trials cannot be considered as necessary for the performance of the public interest tasks vested in the controller by law, the processing of personal data could be "necessary for the purposes of the legitimate interests pursued by the controller or by a third party, except where such interests are overridden by the interests or fundamental rights and freedoms of the data subject" following Article 6(1) (f) GDPR.

2.3 Consent

Under the GDPR, consent must be freely given, specific, informed, unambiguous, and where consent is used as a justification for processing special categories of data, such as health data, such consent must be explicit (Article 9(2) (a) GDPR). Data controllers should pay particular attention to the condition of a "freely given" consent. As stated in the Working Party 29 Guidelines on consent, this element implies real choice and

control for data subjects. Besides, consent should not provide a valid legal ground for the processing of personal data in a specific case where there is a clear imbalance between the data subject and the controller.

Depending on the circumstances of the clinical trial, situations of imbalance of power between the sponsor/investigator and participants may occur. The CTR expressly addresses these risks and requires the investigator to take into account all relevant circumstances, in particular whether the potential subject belongs to an economically or socially disadvantaged group, or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate[15].

As explained in the Guidelines on consent of the Working Party 29, consent will not be the appropriate legal basis in most cases, and other legal bases than consent must be relied upon (see above alternative legal bases).

Q4. What is the difference between informed consent within the meaning of the clinical trial Regulation and consent within the meaning of the GDPR?

The requirement of informed consent by the CTR must not be confused with consent as a legal ground for processing personal data set out in Article 6(1) (a) of the GDPR.

The Clinical Trials Regulation contains several provisions that specify certain aspects on how the processing of personal data should take place. Informed consent required by that Regulation serves as an ethical standard and procedural obligation. The informed consent under CTR is the fundamental condition under which a person can be included into a clinical trial. It is not conceived as an instrument for data processing compliance.

Informed consent, in the context of CTR, is a safeguard not a legal basis for data processing. Therefore, it is important to distinguish between the requirement for consent for a subject to participate in a CT and the requirements for a lawful processing of personal data under the GDPR (see Q&A 3).

Q5. How to understand the requirements of the GDPR regarding information that should be given to subjects participating in a clinical trial?

Any person included in a clinical trial should receive the relevant information related to the clinical trial as required by the CTR as well as the information according to Article 13 of the GDPR, in particular the legal basis for data processing (see Q&A 3).

Q6. What are the legal consequences of withdrawal of the consent for participation in the clinical trial under the Clinical Trial Regulation?

Article 28(3) of the CTR states that withdrawal of the informed consent to participate in a clinical trial shall not affect any activities already carried out and the use of data obtained on the basis of the informed consent before that withdrawal. .

[15] Recital 31 CTR.

Consent for participation in clinical trial must be distinguished from the consent for processing personal data in the context of that clinical trial (see Q&A 4).

The withdrawal of consent to participate in a clinical trial under CTR may not necessarily affect the processing of personal data gathered in the context of that trial. The personal data may continue to be processed where there is an appropriate legal basis for such processing under GDPR. In such cases, the personal data of that person gathered before the withdrawal shall be kept for the purposes and in the conditions defined by the protocol and the legislation. For example, if serious adverse reaction occurs to the patient, the sponsor has the rights to process the data by reporting the data to the national competent authorities (based on the legal obligation of the controller Article 6(1) c of the GDPR in conjunction with Article 9(2)i.

Under the GDPR, if consent is used as the lawful basis for processing (Article 6(1) a), there must be a possibility for individuals to withdraw that consent at any time (Article 7(3)), and there is no exception to this requirement for scientific research provided for under Article 7. As a general rule, if consent for data processing under GDPR is withdrawn, all data processing operations that were based on consent remain lawful in accordance with the GDPR (Article 7(3)); however, the controller shall stop the processing actions concerned and if there is no other lawful basis justifying the retention for further processing, the data should be deleted by the controller (see Article 17(1) (b) and (3) GDPR). In cases where personal data are processed on the basis of consent under GDPR, it is appropriate for the investigator to determine with the trial subject whether their withdrawal of consent under CTR relates solely to participation in trial activities or whether they also withdraw consent to the processing of their data.

However, the withdrawal of consent under the CTR does not affect the processing operations that are based on other lawful grounds, in particular legal obligations to which the sponsor/investigator are subject such as the ones related to safety purposes.

Q7. What is the meaning of Article 28(2) of the CTR and what are the implications for the use of personal data outside the protocol of the clinical trial (secondary use) within the scope of the GDPR?

The CTR explicitly refers to the situation where consent may be sought from the clinical trial subject for the use of personal data concerning that subject outside that clinical trial protocol for future scientific purposes (Article 28(2) of the CTR).

Secondary use of data which is anonymised does not fall within the scope of the GDPR. By contrast, in case of processing of personal (including pseudonymised) data outside of the CT protocol the following must be considered:

If a sponsor/investigator would like to use the personal data gathered for any other purposes than the one defined by the clinical trial protocol (e.g. medical data collected to conduct a clinical trial on breast cancer used to run a study aiming to identify new biomarkers, but which was not foreseen in the clinical trial protocol), it would require a valid legal ground

under Article 6 of the GDPR[16] (see question 3 for the legal basis). The chosen legal basis may or may not differ from the legal basis of the primary use.

Due account must be taken of Article 5(1)(b) of the GDPR which provides for a presumption of compatibility of purposes, subject to the conditions set for in Article 89(1) GDPR, when further processing is carried out for purposes of scientific research. In any event, even when the presumption of compatibility is found to apply , the scientific research making use of the data outside the protocol of the clinical trial must be conducted in compliance with the relevant legal basis and all other relevant applicable provisions of data protection law as stated under Article 28(2) CTR. Therefore, the controller is not exempt from the other obligations under data protection law, for example with regard to fairness, lawfulness, necessity and proportionality, as well as data quality.

Where consent (Article 6(1) (a) of the GDPR) is sought to be used as a legal basis for the processing of personal data for secondary use, the following considerations should be taken into account:

- The GDPR requires that personal data is collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes. Further processing for scientific research purposes shall, in accordance with Article 89(1), not be considered incompatible with the initial purposes (Article 5(1) (b)).
- Pursuant to Article 4(11) of the GDPR, consent of the data subject means any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her[17].
- Pursuant to Article 7(3) of the GDPR, an individual has the right to withdraw his/her consent at any time during the conduct of the clinical trial. Data subjects should be given this information prior to giving consent to participate in the clinical trial.
- As regards consent for processing personal data for the purpose of scientific research, it is further clarified in Recital 33 of the GDPR: "*It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognised ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose."*
- Recital 33 brings some flexibility to the degree of specification of consent and allows that the purpose may be described at a more general level. Yet it must be interpreted in a strict manner and requires a high degree of scrutiny. It should be noted that the obligations with regard to the requirement of specific consent still apply, despite the

[16] The same applies when allowing access to the individual patients' records by third country inspectors.
[17] See also Article 7 of the GDPR for additional general conditions for consent.

flexibility of recital 33. This means that, in principle, scientific research projects can only include personal data on the basis of consent if they have a well-described purpose.

- Therefore, the sponsor may either seek consent of the subject for a secondary use already in the beginning of the clinical trial (the first use). Here it is important to note that this form of consent must strictly be distinguished from the informed consent in the context of the CTR. The sponsor must ask separately for consent of data processing within a secondary use (using different consent sheets) and has to indicate the specific research purposes of this use.
- On the other hand if the aim of using the data for further research outside the protocol of the CT arises after the clinical trial has been completed, the sponsor must go back to the data subjects for specific consent.
- In any case the sponsor/investigator must inform the subject according to Article 13 of the GDPR (e.g. on the legal basis and the right to withdraw consent) (see Q&A5).

Q8. Processing of personal data in the context of emergency clinical trials (Article 35 of the CTR)

Once the strict conditions of Article 35 of the CTR are fulfilled, a subject can be enrolled in a clinical trial in the situation of emergency, exceptionally without any prior informed consent. Following an intervention, the informed consent should be sought from a subject or his or her legal representative as soon as possible in order to maintain the subject in the clinical trial. In case a subject/legal representative does not confirm his/her consent, the participation of the subject cannot be continued.

As the prior informed consent of the subject is only an additional safeguard and not the legal basis for the processing from a data protection perspective, the legal basis for the processing of personal data in the context of emergency clinical trials remains the public interest pursued in Article 6(1) (e) of the GDPR or the legitimate interest pursued in Article 6(1) (f) of the GDPR. In addition, the initial processing, necessary to provide a person with a treatment and to record its outcomes, in the absence of consent in the meaning of Article 28 of the Clinical Trial Regulation, can also be justified on a ground of vital interests of the data subject (Article 35 of the CTR in conjunction with Article 6(1) (d) and Article 9(2) (c) of the GDPR).

In light of Article 35(3) of the CTR in case participation in a trial will not be confirmed by the ex-post informed consent given by that person or his/her legal representative, that person or legal representative should be informed of the right to object to use the data gathered initially. If the person confirms its participation in a trial, data can be further processed for the purpose of that trial.

If a data subject dies before the consent could be confirmed/refused, the processing of that data is no longer covered by the GDPR and the conditions for processing may be determined by national law.

Q9. Is a sponsor established in third country subject to EU data protection rules?

The GDPR applies to controllers and processors established in the EU as well as to controllers and processors not established in the EU where the processing activities are related to the offering of goods or services to data subjects in the EU or the monitoring of their behaviour in the EU (Article 3 GDPR). Where the sponsor processes personal data of data subjects in the EU related to these purposes, including in the context of managing the clinical trial, the GDPR is fully applicable, including the obligation to designate a representative in the EU (Article 27 GDPR).

Q10. What rules apply to the data transfers outside the EU?

Entities in the EU that transfer personal data to an entity outside the EU (e.g. to controllers, processors or other recipients in third countries or to international organisations[18]) have to comply with the rules on international transfers (Chapter V of the GDPR). The GDPR has not changed the rules that already existed under Directive 95/46 (and that have been in place for more than 20 years), but expanded the possibilities to use existing transfer instruments and introduced new transfer tools. This allows EU entities to adopt the approach that is most suitable for their specific situation. Depending on the situation, transfers can for example take place on the basis of an adequacy decision (i.e. where the Commission has decided that a third country or international organisation ensures an adequate level of protection), on the basis of an agreement or arrangement that contains appropriate data protection safeguards (Article 46 GDPR), or on the basis of one of the derogations listed in Article 49 GDPR (e.g. for important reasons of public interest).

Q11. How should a sponsor proceed in the case of clinical trials authorised under the Clinical trials Directive?

For **new clinical trial applications** that will be submitted for authorisation under the clinical trial Directive until the Clinical Trial Regulation enters into application, the sponsor should continue to follow the rules in light of the respective national laws transposing the clinical trials Directive.

In case of clinical trials authorised under the CTD that are **already ongoing** the sponsor should consider the following aspects:

- The legal basis:

The legal basis for processing of personal data in an ongoing clinical trial, authorised on the basis of Directive 2001/20/EC, will not be affected by the entry into application of GDPR e.g. if subjects of a clinical trial were asked for consent for data processing for the purpose of that clinical trial, this cannot be changed into another legal basis. The consent will remain the legal basis for processing of those personal data under the GDPR. If the legal basis was the public interest, this legal basis remains the same.

- In light of Articles 13 and 14 of the GDPR, sponsors may need to provide, where necessary, additional information to the data subject participating in the ongoing clinical trials:

Depending on the information initially provided to the clinical trials participants, some additional information may be required. The requirements on the information to be provided to the data subject are clarified in Articles 13 and 14 of the GDPR. The update of the information that is to be given to the data subject may be necessary, independent of the legal basis for processing of data. The information required by the GDPR should be provided as soon as possible[19].

- Re-consent:

GDPR clarifies the requirement on consent in Articles 4(11) and 7, as well as in recitals 32, 33, 42 and 43. In case consent was chosen as an initial legal basis for personal data processing in the context of the clinical trial, the data controller needs to assess whether the initial consent fulfils the requirements of GDPR. If not, then re-consent may be required.

The data controller needs to consider whether these actions are necessary with regard to the personal data subjects whose data are still being processed in the context of that trial (it is irrelevant whether the person still receives the investigational medicinal product or whether he/she is in follow up phase of a trial).

For other information:

For further detail please consult the data protection authorities established in the Member States.[20]

[19] See recent WP29 guidelines on transparency: http://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=622227, page 18, paragraphs 30-32

[20] https://ec.europa.eu/info/law/law-topic/data-protection/reform/what-are-data-protection-authorities-dpas_en.