Interplay between the EU Clinical Trials Regulation and the GDPR

Clinical trial sponsors should take into account data protection compliance in the early development of the trial to enable its authorization in the EU. By **Laura Brodahl** and **Jan Dhont** of Wilson Sonsini Goodrich & Rosati.

With the entry into application of the European Union's (EU) Clinical Trials Regulation (CTR)[1], an additional emphasis is put on data protection compliance during clinical trials. This article explains the interplay between the CTR and the existing EU data protection rules, followed by a high-level overview of key privacy compliance items that are impacted by the CTR. This article does not address any specific obligations that may be imposed by national laws.

Background

The CTR entered into application on 31 January 2022. It applies to all clinical trials conducted in the EU.[2] In layman terms, a clinical trial is a study performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are carried out on human volunteers.[3]

The CTR repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application. It aims to ensure a harmonized and favourable environment for carrying out clinical research on a large scale, with high standards of transparency and safety for clinical trial participants.

The CTR officially entered into force on 16 June 2014, however, the timing of its application was delayed until the development of an EU-wide clinical trial portal and database (known as the Clinical Trial Information System or CTIS) was completed.[4] The CTR harmonizes the assessment, authorization, and supervision process for clinical trials throughout the EU by requiring sponsors to submit their trial application via the CTIS portal.[5] In addition, the CTIS database aims to increase transparency through making information relating to clinical trials and their results publicly accessible.

Direct interplay between the CTR and the GDPR

The CTR regulates conducting clinical trials by setting forth requirements to ensure that trial subjects' "rights, safety, dignity and well-being [...] are protected" and that trials "generate reliable and robust data."[6] The General Data Protection Regulation (GDPR)[7] ensures the protection of individuals with regard to the processing of their personal data (i.e. any information relating to an identified or identifiable individual), including personal data concerning health. Both legislations apply simultaneously, with the CTR as a sectoral law containing specific provisions relevant from a data protection viewpoint. According to the EDPB, the CTR does not set forth derogations to the GDPR's requirements.[8]

Personal data concerning health includes all data pertaining to the health status of a trial subject which reveal information relating to the past, current or future physical or mental health status of the data subject; a number, symbol or particular assigned to a natural person to uniquely identify the natural person for health purposes; information derived from the testing or examination of a body part or bodily substance, including from genetic data and biological samples; and any information on, for example, a disease, disability, disease risk, medical history, clinical treatment or the physiological or biomedical state of the data subject independent of its source, for example from a physician or other health professional, a hospital, a medical device or an *in vitro* diagnostic test.[9] As a result, the information collected from trial subjects will be subject to the principles of the GDPR. Such is also the case if the trial data is deidentified (or 'pseudonymized') since such data still constitutes personal data under the GDPR.[10]

The required application of the CTR and GDPR in tandem also appears from the texts themselves. On the one hand the CTR provides that the GDPR should be applied to data processing that takes place in the context of clinical trials[11] as well as scientific research making use of data collected for a trial, but which takes place outside the protocol of the clinical trial.[12] In particular, that individuals' data privacy rights should be respected and the EU Member States must take compliance with data protection rules into account when reviewing the assessment report.[13] On the other hand, the GDPR requires that personal data be processed lawfully.[14] This implies that clinical trial data must be processed in compliance with all applicable laws and regulations such as the CTR. Also, the GDPR recitals further add that the processing of personal data for scientific purposes should comply with relevant legislation, such as legislation applicable to clinical trials.[15]

Data protection compliance as a criterion for trial authorization

As was the case under the Clinical Trials Directive,[16] clinical trials are subject to scientific and ethical review and subsequent regulatory authorization before they may be undertaken in the EU.[17] In order to obtain such an authorization under the CTR, the trial sponsor must submit an application dossier to the intended Member States through CTIS.[18]

The application consists of two key

objectives: a review of the scientific and medicinal product information (referred to as "Part I")[19] and a review of the regulatory aspects of the trial, including how the trial will comply with applicable data protection rules (referred to as "Part II").[20] The latter includes providing, among others, (1) a study protocol which covers technical and organizational measures for compliance with data protection principles[21]; (2) a description of the procedures to obtain informed consent from trial subjects[22] and (3) a written statement that data will be processed in accordance with GDPR.[23] This means that sponsors and other involved trial actors, such as contract research organizations (CROs) and investigators, need to consider data protection compliance early on in the development of their trials if they wish to undertake or expand them into the EU.

An important element is that, since the UK's withdrawal from the EU, it has implemented a UK version of the GDPR that largely mirrors the GDPR. At present, this essentially extends the protection of the GDPR still to the UK. However, the CTR will not apply in the UK[24] and it remains to be seen if the UK will adopt similar legislation.

Impact on the qualification as a controller, processor or joint-controller

The main actors involved in a clinical trial are (1) the 'sponsor' (i.e. an individual, company, institution or organization which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial)[25] and (2) the 'investigator' (i.e. an individual responsible for the conduct of a clinical trial at a clinical trial site).[26] Depending on the circumstances of the trial, there may be several investigators, with one acting as the 'principal investigator' (i.e. an investigator who is the responsible leader of a team of investigators).[27]

The GDPR in turn allocates the responsibilities for compliance with the different data protection obligations,[28] and how data subjects can exercise their rights to their personal data in practice, depending on a party's role in the processing.[29] The roles are further laid down in the data protection terms or agreement concluded between the parties.[30] At a high level, the roles are: (1) controller (who determines the purposes and means of the processing, i.e. the why and how of the processing)[31], (2) processor (who processes personal data on behalf of the controller)[32] or (3) joint-controller (who jointly determines the purposes and means of the processing with another controller).[33] As a party's data protection role also impacts its liability for the processing towards trial participants (as data subjects), it is key to determine the role early on.

More specifically, the GDPR applies to (1) controllers and processors established in the EU (e.g. sponsors established in the EU) as well as to (2) controllers and processors not established in the EU, where the processing activities relate to the offering of goods or services to data subjects in the EU or the monitoring of their behaviour in the EU (e.g. sponsors established in the U.S., who are managing a trial in the EU).[34] Although every case must be assessed individually, processing activities performed to conduct a clinical trial typically fall within the 'monitoring' criterion. For example, the EDPB clarified that this criterion encompasses "monitoring or regular reporting on an individual's health status".[35]

The data protection role of the parties involved in a clinical trial is however not always clear-cut. Neither the GDPR nor CTR specifically allocate data protection roles in the trial context and various EU supervisory authorities have taken diverging views on how to qualify trial actors under data protection law. In practice, parties should assess and determine their respective data protection role (controller, processor, joint controller) on a case-by-case basis depending on their responsibilities in the concerned trial (e.g. trial sponsor, drug manufacturer, health care provider or CRO).

Notably, the European Data Protection Board (EDPB) considers that a sponsor will typically act as a controller, whereas an investigator may be a processor of the sponsor or a joint controller together with the sponsor. Practically, the latter is likely the case where the parties collaborate together in the drafting of the study protocol (i.e. the purposes, methodology/ design of the study, data to be collected, subject exclusion/inclusion criteria, database reuse, etc.).[36] However, such is not always the case in practice, and it may be that although both parties collaborate on the protocol, only one has a critical say in the purposes and means of clinical trial processing.

Further, the processing of trial participants' personal data for the purpose of the clinical research is to be distinguished from the processing of the same data for patient care. In the latter case, the investigator (e.g. hospital) will remain a separate controller from the sponsor.[37] In the event that the investigator does not participate in the drafting of the protocol (rather they just accept a protocol provided to them by the sponsor), and the protocol is only designed by the sponsor, the investigator should be considered a processor of the sponsor.

It is noteworthy that the EDPB plans to provide further guidance in relation to data protection roles and clinical trials in its forthcoming guidelines on processing for medical and scientific research purposes.[38]

Strengthening the legal basis for processing in clinical trials

The controller must ensure that the processing complies with the GDPR, including determining the most appropriate legal basis.[39] In a clinical trial context, the EDPB considers that there are two main processing activities that may each require a different legal basis: (1) processing for reliability and safety related purposes and (2) processing for performing the scientific research, as explained below.[40]

The EDPB is of the opinion that processing operations expressly provided by the CTR related to reliability (e.g. archiving the clinical trial master file and the medical files of subjects[41], disclosure of trial data during regulatory inspections[42]) and safety purposes (e.g. reporting adverse events)[43] may fall within legal obligation(s) to which the controller is subject.[44] Therefore, such processing should be considered necessary to comply with legal obligations to which the sponsor or investigator are subject.

The processing for research activities[45] (e.g. conducting patient

monitoring and related analyses) may either be based on the data subject's explicit consent[46], a task carried out in the public interest[47], or the legitimate interests of the controller.[48] However, the EDPB notes that consent is not an appropriate legal basis if there is a clear imbalance of power between the data subject and the controller. In such a case, it is believed that it is hard for consent to be "freely given". Such an imbalance may exist depending on the circumstances, for instance, when the data subject is not in a good health condition and there is no available therapeutic treatment outside the clinical trial.[49] This concern is echoed in the CTR with respect to ensuring valid trial consents, as it requires the investigator to take into account 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 their decision to participate.[50]

In addition to ensuring a legal basis for the processing under the GDPR, the sponsor must also obtain trial participants' written 'informed consent' prior to the start of any clinical trial as an ethical and procedural obligation under the CTR.[51] The CTR applies similar criteria as the GDPR for such a consent to be valid (e.g. the consent must be freely given, informed and requires an action from the trial subject).[52] Therefore, also relying on consent for the processing of patient data for research purposes will in many situations be the most practical approach for sponsors and most transparent towards trial participants. In practice, it is important that the consent form distinguishes between the consent provided to perform the clinical trial and the consent provided to enable the processing of the participant's personal data.

REFERENCES

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. 1–76.
2 Art. 1 CTR.
3 See also the definition of 'clinical trial' in art. 2.2 CTR.
4 Art. 82(3) jo 99 CTR. The CTR entered into application 6 months after the independent audit report, approving the CTIS, was published.
5 More information about the use of CTIS can be found in the European Medicines Agency's Clinical Trials Information System (CTIS) - Sponsor Handbook, available at https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_.pdf
6 Art. 3 CTR.
7 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJEU L 119 04/05/2016.
8 European Data Protection Board Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b)) (adopted on 23 January 2019), page 3.
9 Recital 35 jo Art. 4.15 GDPR.
10 Art. 4.5 GDPR.
11 Art.28.1(d) CTR. Note that the CTR refers to Directive 95/46/EC, which was repealed and replaced by the GDPR.
12 Art. 28.2 (in fine) CTR.
13 Recital 76 CTR and Art. 7.1(d) CTR.
14 Art. 5.1 (a) GDPR.
15 Recital 156 and recital 161 GDPR.
16 Art. 9 Clinical Trial Directive.
17 Art. 4 CTR.
18 Art. 5 CTR.
19 Art. 6 CTR.
20 Art. 7.1(d) CTR.
21 Annex I (application dossier for the initial application) point D "protocol", (x), (z), (ak), (al) and (am).
22 Annex I (application dossier for the initial application) point L "subject information, informed consent form and informed consent procedure (information per Member State concerned)".
23 Annex I (application dossier for the initial application) point R "proof that data will be processed in compliance with Union law on data protection".
24 The UK Government has launched a public consultation on possible changes to its clinical trials legislation, available at https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials. The consultation closes on March 14, 2022.
25 Art. 2.14 CTR.
26 Art. 2.15 CTR.
27 Art. 2.16 CTR.
28 For example, ensuring a legal ground for the processing – such as the individual's consent, providing notice to individuals, information security and performing data protection risk assessments.
29 EDPB Guidelines 07/2020 on the concepts of controller and processor in the GDPR Version 2.0 (adopted on July 7, 2021), page 3.
30 Art. 26 and 28 GDPR.
31 Art. 4.7 GDPR.
32 Art. 4.8 GDPR.
33 Art. 26 GDPR.
34 Art. 3.2 GDPR.
35 EDPB Guidelines 3/2018 on the territorial scope of the GDPR (Article 3) Version 2.1 (adopted on 12 November 2019) page 20.
36 EDPB Guidelines 07/2020, page 23.
37 EDPB Guidelines 07/2020, page 23.
38 EDPB Guidelines 07/2020, footnote 31.
39 Art. 6 GDPR or art. 9 GDPR (where the personal data concerns a 'special category' of personal data, such data concerning health).
40 EDPB Opinion 3/2019, §9.
41 Art. 57-58 CTR.
42 Art. 78 CTR.
43 Art. 41-43 CTR.
44 Article 6.1(c) GDPR.
45 The EDPB defines 'scientific research' in this context as any research project set up in accordance with relevant sector-related methodological and ethical standards, in conformity with good practice.
46 Art. 6.1(a) jo 9.2(a) GDPR, if all the conditions for a valid consent can be met in the specific circumstances of that trial.
47 Recital 45 GDPR; Art. 6.1(e) jo 9.2(i) GDPR, such as when clinical trials are performed for reasons of public interest in the area of public health on the basis of Member State law (e.g., in the context of developing vaccines during the COVID-19 pandemic).
48 Art. 6.1(f) jo 9.2(i) or (j) GDPR.
49 EDPB Document on response to the request from the European Commission for clarifications on the consistent application of the GDPR, focusing on health research (adopted on 2 February 2021), §8.
50 Recital 31 CTR.
51 Art. 28.1(c) jo 29 CTR.
52 Recital 27 jo recital 30 jo Art. 28 CTR.
53 Art. 5.2 jo 24 jo 32 GDPR.
54 Art. 56 CTR.
55 Annex 1 (Application Dossier for the Initial Application) D.17 (am).

Re-affirming technical and organizational measures

The GDPR requires a controller (sponsor and/or investigator) to implement appropriate technical and organizational measures to ensure and be able to demonstrate that the personal data are processed in accordance with the data protection rules.[53] While the CTR does not impose any specific information security obligations, it does require having appropriate technical and organizational measures to ensure compliance with data protection rules and principles (e.g. data quality, confidentiality and integrity of data).

For example, all trial information must be stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted, and verified while the confidentiality of the personal data of the subjects remains protected. Appropriate technical and organizational measures to prevent data breach must also be implemented[54] and sponsors must include a description of measures that will be implemented in case of data security breach to mitigate the possible adverse effects, in the study protocol.[55]

Conclusion

The CTR re-affirms and further strengthens the data protection obligations to be applied under the GDPR when conducting a clinical trial in the EU (e.g. transparency to data subjects, data quality and confidentiality, data subject rights). In particular, sponsors must demonstrate how such data protection compliance is and will be ensured in order to obtain the regulatory approval to run a trial in the EU (e.g. through provisions in the study protocol, technical and organizational measures, such as internal policies and procedures, appropriate consent forms and privacy notices). Therefore, both sponsors and investigators should now already consider how to address their data protection obligations in the earliest stages of development of the clinical trial.

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UK CONSULTS ON CLINICAL TRIALS

The government is currently consulting on proposals for legislative changes regarding clinical trials. The proposals are to update the current UK legislation that governs clinical trials, The Medicines for Human Use (Clinical Trials) Regulations 2004" (SI 2004/1031), as amended, which transposes the EU Clinical Trials Directive 2001/20 EC into UK law.

The aim is to update and strengthen the current clinical trial legislation to:

- Promote public health and ensure protection of participants remains at the heart of legislation
- Remove obstacles to innovation, whilst maintaining robust oversight of the safety of trials
- Streamline the regulation of clinical trials and reduce unnecessary burden to those running trials by embedding risk proportionality into the framework
- Facilitate the evaluation and development of new or better medicines to reduce the burden of disease on patients and society
- Ensure the legislation builds international interoperability so that the UK remains a preferred site to conduct multi-national trials.

On transparency, it is proposed that, in line with international standards, there will be a requirement to register a trial in a World Health Organization compliant public register prior to its start and to publish a summary of results within 12 months of the end of the trial, unless a deferral is agreed by or on behalf of the Research Ethics Committee.

It would also be a requirement to ensure that the protection of participants remains at the heart of legislation. Clinical trial findings would be shared with participants in a suitable format within 12 months of the end of the trial, or explain why this is not appropriate.

There are also new proposals regarding obtaining informed consent in cluster trials.

"Under the current legislation, 'cluster' trials with groups rather than individuals, can only be overtaken if every participant actively provides their written consent after being given detailed information about the trial in an interview with one of the investigators. Simplifying the way that informed consent can be obtained for cluster trials will support and promote their use and facilitate the gathering of real-world data to inform best practice in a way that is more proportionate to the low level of risk involved. This approach should encourage wider uptake into lower risk trials. The introduction of this simplified means of seeking agreement from participants will make these types of low intervention trials more feasible and therefore widen the reach and participation of this type of research."

• *This consultation closes on 14 March. See www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials*

ICO consults on research provisions in the UK GDPR and the DP Act

The ICO is seeking comments on its draft guidance on research provisions.

"The aim of the guidance is to highlight where in the legislation the various provisions that relate to research can be found, how they fit together and their practical effect. It also provides guidance on the definition of key terms, which will help organisations understand when they can rely on the research provisions."

"The guidance is intended to provide more detail and clarity about this complicated area of data protection. It will help those engaged in research to carry out their processing while being compliant with the law. It should give researchers confidence to make use of the provisions where appropriate," the ICO says.

• *The consultation is open until 22 April 2022. See ico.org.uk/about-the-ico/ico-and-stakeholder-consultations/draft-gdpr-research-provisions/*