

Ethical review of patient safety and public health in EU clinical trials legislation: impact of COVID-19 pandemic

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Abstract

Purpose: The study considers the ethical review of the European Union (EU) clinical trials (CTs) legislation, namely the Clinical Trials Regulation (CTR) (EU) 2014/536, the Directive 2001/20/EC and the “Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic” (GMCT) (version 3) issued on 28 April 2020 by the European authorities in the field. **Background:** The Directive 2001/20/EC focuses the legal provisions for the conduct of CTs by acknowledging the screening role of the Ethics Committees (ECs) and of the national competent authorities (NCA) in the Member States (MS) to protect the CT subject and the personal data. **Content:** The present article displays the ethical requirements for conducting, monitoring and reporting of the CTs by raising awareness on the: (i) new conceptual framework of the “clinical trial”, “low-intervention clinical trial”, “non-interventional study” and “ethics committee”; (ii) ethical considerations addressed in Part I and Part II of the assessment report; (iii) evaluation of the coronavirus disease 2019 (COVID-19) pandemic on the current regulatory framework. **Conclusions:** The CTR stimulates the EU clinical research and enables an independent control with regard to the respect of the interests of the CT subject.

Keywords: clinical trials, patient safety, ethics committees, European Union, COVID-19 pandemic.

Introduction

The Regulation 2014/536 issued by the European Parliament and the Council on 16 April 2014 on medicinal products (MPs) for human use enables a harmonized framework of the legal provisions governing the clinical trials (CTs) at the European Union (EU) level [1]. The Regulation is set to replace the Clinical Trials Directive 2001/20/EC (CTD) [2] adopted in accordance with the 1996 version of the Declaration of Helsinki regarding the ethical framework of the principles and provisions for the medical research. This approach to the ethical principles refers to human subjects (HS) and it was launched by the *World Medical Association* (WMA). During the transitional period, in order to facilitate the implementation of the new legal provisions governing the CTs, the Clinical Trial Regulation (CTR) allows sponsors “to conduct a clinical trial” according to the legal provisions of the CTD (Recital 79 CTR).

As regards the harmonized approach to the new conceptual framework, the study indicates the existing definition of the “clinical study” (CS) launched by the CTD and the “advantages for sponsors and investigators” (Recital 5 CTR). It should be noted that the CTD is not applicable to non-interventional studies (NIS) (Article 1 CTD) suggesting a particular difficulty to launch a CT in the Member States (MS) (Recital 4 CTR). Thus, with the aim to harmonize the legal dispositions at EU level, Recital 3 of the CTR launches a broader understanding of the concept of “clinical study” and a new approach to the international provisions and the EU law in the field of the MPs. Furthermore, it should be noted that the CTD also focuses the principles of the good clinical practice, the protection of the interests of the CT subject

and the screening role of the ethics committees (ECs) and of the national competent authorities (NCA) [Recital 2 and Article 3(2)(a) CTR]. Nevertheless, some aspects should be carefully analyzed considered such as the timing of the application of the CTR. This depends on the functionality of the EU database at EU level containing “the data and information submitted in accordance” with the CTR and enabling the citizens of the EU to be informed concerning the CT information and related aspects of the MPs [Article 81(1)(2)(3)(4) CTR].

Therefore, the *European Medicines Agency* (EMA) delivered in March 2015 a set of specific guidelines concerning the functionality of the EU portal and of the EU database in accordance with the legal basis of the Article 82 of the CTR and providing specific requirements for the submission through the EU portal and EU database [3]. An Appendix on disclosure rules launched on 2 October 2015 established clear specifications for the MS experts (here including the ECs members) arguing particular details for the inclusion in the database by considering the legal provisions of the Article 81 CTR [4].

In December 2015, EMA established a new timeline for the EU portal and EU Database “which will be subject to the independent audit” [5]. The European Commission adopted on 8 December 2017 the detailed Guidelines on good manufacturing practice for investigational products for human use focusing in Part 1, entitled “Scope”, the protection and safety of the subject and the accuracy of the data issued in the CTs [6] and in Part 6, entitled “Production”, the respect of the scientific norms and technical rules [6]. Regarding the development of the Clinical Trials Information System (CTIS) required by the CTR, the EMA Management Board delivered a press

release on 4 October 2019 addressing a monitoring report and assessing the CTIS functionalities [7].

☞ **Definitions of “clinical trial”, “low-intervention clinical trial”, “non-interventional study” and “ethics committee”**

The CTR clarifies the definitions of the “clinical trial”, the “low-intervention clinical trial” and the “ethics committee”. Moreover, the new EU CTR focuses a new conceptual design and new measures with aim to “increase Europe’s competitiveness in clinical research” [8] and for larger transparency concerning the information provided during the CTs [9].

The definition of the “clinical trial” is clarified in accordance with the new regulatory framework of the CTR by introduction a broader approach to the international provisions and the EU legal guidelines regulating the MPs (Recital 2 CTR). An in-depth observation takes into consideration “the dichotomy of ‘clinical trial’ and ‘non-interventional study’” according to the clarifications of the Recital 3 of the CTR. Moreover, Recital 4 and Recital 5 of the CTR develop an integrative approach of the CTR focusing: the role of the patient populations, the genomic information, the “new procedures for the submission of an application”, the submission “through a single portal” of one “application dossier” for the CTs, the procedure and the timelines for the CTs as a “major challenge for all stakeholders” [10].

Nonetheless, the definition of the “clinical trial” focuses three main conditions in accordance with the regulatory framework of the Article 2(2)(a)(b)(c) of the CTR namely: (i) the particular therapeutic strategy [Article 2(2)(a) CTR]; (ii) the focus on the investigational medicinal products (IMPs) and the decision to admit the HS in a CS [Article 2(2)(b) CTR]; (iii) the diagnostic or the monitoring procedure applied to the normal clinical practice (NCP) [Article 2(2)(c) CTR].

The “non-interventional study” is presented in the CTR as a CS “other than a clinical trial” [Article 2(3)(a)(b)(c) CTR]. In this direction, Article 1 mentions that the legal framework of the CTR “does not apply to non-interventional studies”. However, the CTR establishes “a clear distinction” [11] by introducing for the first time the definition of the concept of the “low-intervention clinical trial” [12, 13]. Moreover, with the aim to optimize the MPs in question and to contribute to the public health framework, the CTR develops the definition of the “low-intervention clinical trial”, by mapping a set of three conditions to fulfill for the CTs: (i) the authorization of the IMPs “excluding placebo” [Article 2(3)(a) CTR]; (ii) the use of the IMPs following the status of the marketing authorization [Article 2(3)(b)(i) CTR]; (iii) the use of the IMPs considering the “safety and efficacy” in all MS of the EU [Article 2(3)(b)(ii) CTR].

By opting to associate both legal provisions of the use of the IMPs in accordance with the marketing authorization and the principles of the safety and efficacy of the IMPs in all MS, Article 2(b) considers for first time that the risks and challenges for the trial participant (TP) “cannot be the same when the treatment applied is similar to that of

routine clinical practice, *i.e.*, when the medicinal product has had a marketing authorization for several years” [11].

In agreement with the international provisions in the field of the conduct of the CTs, related studies focus “key scientific principles” [14]. Furthermore, the CTR sought to enable fundamental provisions concerning the “involvement of ethics committee” (Recital 18, CTR). In this direction, one particular observation addressed is “the accordance” with the national provisions of the MS empowering the ECs “to give opinions” considering the regulatory framework of the CTR [Article 2(2)(11) CTR]. Thus, the Regulation states the role of the ECs during the authorization of CTs considering the opinions of laypersons here including: (i) the patients; (ii) the organizations representing the patients [Recital 18 and Article 2(2)(11) CTR]. Moreover, the CTR requires a specific conceptual and organizational design that responds to the purposes of the CTR by setting an eight-dimensional approach: (i) “the timelines for the authorisation of that clinical trial” (Recital 18 CTR); (ii) the national organisation and the law of the MS (Recital 18, Recital 30, Recital 32, Recital 74 and Recital 77 CTR); (iii) the presence of the laypersons, here including the patients’ organizations [Recital 18, Recital 39, Recital 67, Article 9(3), Article 29(2)(a)(iv) CTR]; (iv) the determination of “the appropriate body or bodies” (Recital 18 CTR); (v) the respect of the international guidelines (Recital 18 CTR); (vi) the assessment of a “reasonable number of persons” (Recital 18 CTR); (vii) the requirement for the “necessary qualifications and experience” (Recital 18 CTR); (viii) the independence of “the persons assessing the application” (Recital 18 CTR); (ix) the submission of opinions and views in accordance with the aims of the CTR (Recital 11, Recital 68, Article 2(2)(11) CTR).

The new Regulation facilitates the creation of a harmonized regulatory framework for the protection of the patient safety and public health. The CTR thus introduces a complex harmonization of the rules and procedures for the CTs “in order to avoid administrative delays” (Recital 7 CTR). These general provisions include also an important “increase in transparency” on “data related to clinical trial” and “personal data generated” [11] here including that all data generated within the CTs to be recorded in a database free and accessible for the public (Recital 25 CTR). Therefore, the new legal provisions focus the principles of transparency, the confidentiality of records and the protection of personal data.

☞ **ECs: ethical and scientific review**

Moreover, the CTR lists two main criteria of the reform of the ECs namely “the ethical and scientific evaluation” [11], as the CTR involves an increased role for the ECs. Moreover, the recent literature argues the importance of the ethical governance of the medical research pointing the approach to the data protection and the health policy in EU [15, 16].

In order to involve the ECs in the ethical and scientific evaluation, the legal provisions of the CTR argue that the ECs “will have to interact with the Single Portal of the European Medicines Agency” [11]. Furthermore, the CTR details the role of the MS to select the convenient body (bodies) to be included in the appraisal of an

application and to manage the participation of the ECs in accordance with the timelines enabled for the authorization of the CTs and the purposes of the CTR (Recital 18 CTR). Under the new regulatory framework, the authorization procedure “is largely controlled” by MS (Recital 70 and Article 4 CTR) as the CT “shall be subject to scientific and ethical review” (Article 4 CTR) following: (i) the respect of the ethical principles while considering the deliberations for the marketing authorization [17] and (iii) the “existing systems of ethics review” [18].

The evaluation procedure established for the CTR engages the following five aspects: (i) a reporting MS [Article 5(1) CTR]; (ii) the situations regarding the acceptance of the proposal of the sponsor [Article 5(1) CTR]; (iii) the conditions of the low-intervention CT [Article 5(2) CTR]; (iv) the validation of the application [Article 5(3) CTR]; (v) the decision on the clinical trial [Article 8(1)(2) CTR]. Moreover, the CTR addresses two sections of the evaluation report – Part I and Part II – with the aim to ensure “quick access to new, innovative treatments” (Recital 8 CTR).

Part I focuses the following issues: the public health approach pointing the characteristics of the IMPs [Article 6(1)(b)(i) CTR] and the relevance of the CTR [Article 6(1)(b)(i) CTR], including the importance of the subjects taking part in the CTR; the risks and challenges for the subject here including: the approach to the IMPs, the comparative evaluation of the intervention to NCP, the safety measures, the “monitoring, safety reporting, and the safety plan” [Article 6(1)(b)(ii) CTR] and the evaluation of the risks associated to the medical condition concerning the health of CTs subject.

Part II of the evaluation process considers the following requirements: the informed consent in accordance with the legal provisions of the Chapter V CTR; the conditions for “rewarding or compensating subject” according to the regulatory framework of the Chapter V “Protection of subjects and informed consent” (Articles 28–35 CTR); the objectivity of the recruitment of the subjects; the legal compliance with the Directive 95/46/EC, the legal dispositions of the Article 49, Article 50 and Article 76 CTR and the approach to the procedure of managing the biological samples of the HS [Article 7(1)(a–h) CTR].

Other recent studies also pointed the role of the EU ethical rules focusing the Regulation (2017/745), namely: (i) the phases of the clinical investigation; (ii) the patient condition and needs [19]. Under the new regulatory framework of the Chapter V of the CTR focusing the protection of the HS and the legal provisions of the informed consent, Article 28(1)(a–h) details the general rules of the CTs by taking into account the following regulatory developments: the public health; the conditions of the informed consent; the “physical and mental integrity”; the “privacy and protection of data”; the “medical care”.

☞ **CTR security communication and clinical information**

Other important contextual area of the new CTR rules states the cooperation between the NCA of the MS concerned in accordance with the purposes of the CTR [Article 81(2) CTR]. In this direction, the EU database established by CTR at EU level will develop the

communication between all interested parts for the authorization of CTs [Article 81(2) CTR]. A third dimension refers to EU citizens in order “to have access to clinical information” about MPs [Article 81(2) CTR]. The EU database will protect the “confidential communication” between the MS with regard to the phase of “the preparation of the assessment report” [Article 81(4)(c) CTR] as one of the major challenges of the new CTR is to focus the promotion of cooperation and engagement during the CS [9]. Moreover, the mentioned and discussed legal provisions concerning communication and clinical information are detailed in: (i) Article 74(1)(2) CTR (“Legal representative of the sponsor in the Union”; (ii) Recital 40 CTR [“relevant safety information” and report of serious adverse events (SAE)]; (iii) Recital 41 CTR (the reporting of safety information on SAE); (iv) Article 41(1)(2)(3)(4) CTRs [adverse events (AE) or “laboratory abnormalities”, the “impact of the benefit–risk balance”, “the causal relationship” to IMP of the CTs]; (v) Annex I “Application dossier for the initial application”, Point D(19)(a & b) CTR (“notification” of AE); (vi) Annex III “Safety reporting”, Point 1 (“reporting” of SAE and “monitoring” of subjects for AE).

☞ **Patient safety and patient care: methodological framework of ongoing CTs during the coronavirus disease 2019 (COVID-19)**

In the context of the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, a methodological guidance pointing the effects in the case of ongoing trials (a draft version launched for consultation on 25 March 2020 to 25 April 2020, agreed by the Biostatistics Working Party and adopted by the Committee for Human Products, the EMA Committee responsible for human medicines) acknowledges the “impact of the coronavirus disease (COVID-19) on trial participants” [20]. The guidance is set for a four-week public consultation and it develops four approaches concerning the “patient safety” and “patient care”, as follows: (i) “an ethical mandate to proceed with the trials during this period; (ii) the integration of all ethical, medical and methodological issues by the sponsors in the decision making; (iii) the risk assessment during the “monitoring activities” of the CTs; (iv) the respect of the local legal provisions in conducting the CTs and the approval by the ECs. Moreover, it should be considered the complex activity of the ECs and other authorities involved during this period [21–24]. Nevertheless, in the context of the COVID-19, the ECs point a set of priority activities by focusing: (i) the review of the CTs submissions [21]; (ii) the benefits from the research “given the context of the social distancing and lockdowns; (iii) a common international action [25] and (iv) the most challenging aspects to global public health, namely the “ethical, social, and legal questions” [26].

☞ **Ethical approach to EMA instruction during the COVID-19 pandemic (April 2020)**

On 28 April 2020, concrete Guidelines were launched by EMA and related medical authorities, namely the

“Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic” (GMCT) (version 3) [27] pointing: (i) the changes to ongoing trials during the COVID-19 pandemic (“Changes to Ongoing Trials”, Chapter 3 GMCT); (ii) the need measures concerning the changes in the principal investigator (PI) to be submitted to the NCA and the ECs (“Changes to Ongoing Trials”, Chapter 3 GMCT); (iii) the specific conditions related to the COVID-19 pandemic at different levels in MS [“Communication with Authorities”, Chapter 6(a) GMCTs]; (iv) the capacity of the ECs during this period and the challenges of the submission process [“Communication with Authorities”, Chapter 6(b) GMCT]; (v) the requirements presented by the sponsor to the NCA and ECs in the context of the changes involving the risk situations (“Communication with Authorities”, Chapter 6 GMCT); (vi) changes to informed consent needed to be considered and approved by the ECs (“Changes to informed Consent”, Chapter 8 GMCT); (vii) certain measures regarding the social distancing or specific situations facing the health care professionals [“Communication with Authorities”, Chapter 6(c) GMCT]; (viii) the requirement for the sponsors to provide to the NCA and ECs the necessary changes [“Communication with Authorities”, Chapter 6(c) GMCT]; (ix) new rules concerning the communication between all parts involved in the CTs here including the notification to the NCA and the ECs (Chapter 7 GMCT).

The new GMCT lays dawn new rules concerning the protection of patient safety and public health, namely: (i) the impact on the physical integrity of the HS and (ii) the impact on the mental integrity of the HS, focusing the challenges associated with the “amendments of documents/information” as part of the CTs application dossier [“Communication with Authorities”, Chapter 6(1) GMCT].

On the other hand, the GMCT remotes source data verification (SDV) for the CTs by focusing: (i) the treatment of the COVID-19; (ii) the prevention of COVID-19; (iii) the final data for trials involving “serious or life-threatening conditions with no satisfactory option” [“Changes to Monitoring”, Chapter 11(d) GMCT].

In addition, the GMCT establishes new approaches to benefit–risk aspects and extraordinary measures during the period of the COVID-19 pandemic related to a harmonized guidance to trial participants (“Changes to Ongoing Trials”, Chapter 3 GMCT) considering the following aspects: (i) the “trial participant safety or the integrity of the trial” (“Changes to Ongoing Trials”, Chapter 3 GMCT); (ii) the “data integrity and protection of personal data” (“Changes to Ongoing Trials”, Chapter 3 GMCT); (iii) the special measures concerning the trial participants in self-isolation or in quarantine (“Introduction”, GMCT); (iv) “the health and safety of the trial participant” (“Introduction”, GMCT); (v) the “well-being” and the “interests” of the trial participants (“Changes to Ongoing Trials”, Chapter 3 GMCT); (vi) the conditions of the “oral consents” “via phone or video-calls” “supplemented with e-mail confirmation” (“Changes to Informed Consent”, Chapter 8 GMCT); (vii) the screening of the treatment performances and efficacy (Chapter 10 GMCT); (viii) the protection of the rights while enabling remote SDV (Annex 1 GMCT); (ix) the trial participants medical records and data (Annex 1 GMCT).

The GMCT also covers the assessment of the changes in the informed consent procedure (“Changes to Informed Consent”, Chapter 8 GMCT) with special attention to: (i) the review and approval of the ECs “in advance”; (ii) the differences between the national legal provisions and the involvement of new trial participants in ongoing CTs with the aim to prevent or treat COVID-19 and related illnesses; (iii) the oral consent in accordance with the Article 2(j) of the CTD “in the presence of an impartial witness”.

Regarding other relevant guidance modifications, the GMCT sets five specific provisions with regard to the COVID-19 patients involved in trials (“Changes to Informed Consent”, Chapter 8 GMCT), namely the: (i) informed consent forms; (ii) the re-consent “for already” trial participants; (iii) the national rules; (iv) the medical condition of the incapacitated adults; (v) the “normal consent procedures”.

☞ Conclusions

The article reviews the impact of the pandemic on the ongoing CTs by focusing the CTs legislation and the increasing role of the ECs here pointing the review of COVID-19 trial submissions. Nevertheless, the new regulatory framework of the CTR and the recent guidance adopted in the context of COVID-19 take into consideration an increase of the necessary actions to protect patient safety and public health.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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