

Ethical governance of the medical research: clinical investigation and informed consent under the new EU Medical Devices Regulation (2017/745)

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Abstract

Purpose: The paper focuses on the ethical appraisal of the clinical investigations (CIs) and the informed consent within the new European Union (EU) legislation on medical devices (MDs). The Regulation (EU) 2017/745 of the European Parliament and of the Council was adopted on 5 April 2017 and entered into force on 25 May 2017, repealing the Council Directives concerning Medical Devices 93/42/EEC and the Active Implantable Medical Devices 90/385/EEC. **Background:** For the past thirty years, the EU legislation on MDs has been updated by several directives: Council Directive 90/385/EEC on Active Medical Devices (1990); Council Directive 93/42/EEC on Medical Devices (1993) and Council Directive 98/79/EC on *In Vitro* Medical Devices (1998) aiming to frame the MDs market development. **Content:** From the ethical perspective, the present article investigates the new rules concerning the CIs of the MDs for human use and accessories for such devices conducted in the EU by highlighting new regulatory aspects: (1) the framework of the clinical evaluation and CI; (2) the relevant definitions; (3) the ethical principles related to CIs; (4) the informed consent; (5) the role of the national ethics committees. **Conclusions:** Although the new guidelines enable an extension of the definition of "medical device" and the harmonization of the rules for "the placing on market and putting into service of the medical devices", it also regulates the MDs industry to ensure clinical benefits for patients and high standards of quality and safety.

Keywords: clinical investigation, clinical evaluation, informed consent, medical devices, European Union.

Introduction

In the European Union (EU), the medical devices (MDs) market was regulated by a complex legislation here including: Regulation (EU) 2017/745 of the European Parliament and of the Council [1], Council Directive concerning Medical Devices 93/42/EEC [2] and the Active Implantable Medical Devices 90/385/EEC [3], Council Directive 98/79/EC on *In Vitro* Medical Devices (1998) [4]. The Regulation (EU) 2017/745 of the European Parliament and of the Council entered into force 20 days following the publication in the *Official Journal of the European Union* on 5 April 2017 amending the Directive 2001/83/EC on the Community Code relating medicinal products for human use [5], the Regulation (EC) No. 178/2002 of the European Parliament and of the Council on food law [6] and the Regulation No. 1223/2009 of the European Parliament and of the Council on cosmetic products [7]. Note that there is a transitional period of three years for organizational measures to be made. Therefore, the paper appraises the major advances concerning the clinical evaluation and clinical investigation (CI) on MDs, protection of public health and patient safety, the confidentiality of data and information and data protection.

The new Medical Devices Regulation (MDR) will be "directly enforceable" in all EU Member States (MS) setting the revised definition of the "medical device" and "an extensive list of classification criteria (Annex VIII)" [8]. Accordingly, it aims to expand the existing definitions

of the term "medical device" and to reclassify "the implantable devices and long-term surgically invasive devices" to Class III (e.g., "surgical disc" and "surgical meshes") (MDR Annex VIII) [9].

The ethical appraisal of the CIs, protection of public health and the patient safety in the new EU MDR (2017/745) addresses the gaps of the past legislation and research, the comparative aspects of the MDs provisions in the EU and United States and the major innovations of the medical research [10, 11]. Furthermore, the ethical approach to the new Regulation points the following key elements: (1) the conduct of a CI considering the clinical evaluation of the MD; (2) the subject's rights and the protection of the patient; (3) the availability of the CI data on the European database on MDs (Eudamed); (4) the involvement of the ethics committees at national level; (5) the "scientific and ethical review" of the CI according to the national legislation [Article 62(3)].

MDR's ethical principles for medical research

Arguably, the adoption of the new EU Regulation states the recognition of the "ethical principles for medical research" in the clinical investigation plan (CIP) involving: (1) humans and (2) the recognition and adoption of the "good clinical practice" referring to the CIs of the MDs and the "applicable regulatory requirements" (Annex XV). In this context, the research reviews the relevant reforms of the new regulatory platform by conducting a systematic

evaluation of the general and additional requirements regarding the CIs “in order to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations” [Article 82(2)]. To address these aspects, the MDR indicates the rules concerning “the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices” in the EU by harmonizing the regulatory framework as regards the MDs for the high-level protection of public health and patient safety [Article 1(1)].

The MDR current provisions provide the key designation of the CIs under the “scientific and ethical review” “performed in accordance with national law” [Article 62(3)]. Three elements are presented as necessary to improve the existent legal device: (i) “the procedures for review by ethics committees” provided by the MS [Article 62(3)]; (ii) the compatibility between the procedures set out by the ethics committees and by the MDR “for the assessment of the application for authorization of a clinical investigation” [Article 62(3)]; (iii) the representation of at least one lay person in the ethical review [Article 62(3)].

☞ MDR’s definitions and regulatory framework

To meet the purposes of the MDR, Article 2 brings significant regulatory changes in the light of the EU complex market, the latest needs of the medical research and the challenges of the approval of the high-risk devices [12] focusing: (I) the definition of the terms: “medical device” [Article 2(1)]; “clinical evaluation” [Article 2(44)]; “clinical investigation” [Article 2(45)]; “clinical investigation plan” [Article 2(47)]; “clinical data” [Article 2(48)]; “subject” [Article 2(50)]; “investigator” [Article 2(54)]; “informed consent” [Article 2(55)]; “ethics committee” [Article 2(56)]; “adverse event” [Article 2(57)]; “serious adverse event” [Article 2(58)].

To regulate the complex and innovative EU market, the new MDR 2017/785 expands the definition of the “medical device” to “any instrument, apparatus, appliance, software, implant, reagent, material or other material” for human usage considering particular medical purposes, such as: diagnosis and prevention of disease here including the products used for “cleaning, disinfection or sterilisation” [Article 2(1)].

The MDR also aligns the regulatory elements governing the clinical evaluation, the CI, the clinical data and the CIP. Awareness of the new provisions will need to set a specific set of elements for: “clinical evaluation”; “clinical investigation”; “clinical data”; “subject”; “informed consent” and “ethics committees”.

A particular consideration will have to be given regarding the clinical evaluation. The “clinical evaluation” is defined as “a systematic and planned process” collecting, analyzing and assessing “the clinical data pertaining to a device” with the aim to verify “the safety and performance” of the device [MDR Article 2(44)]. Recital 29 of the MDR reinforces the regulatory framework of the clinical evaluation by incorporating it “into the enacting provisions to facilitate its application”. Furthermore, the clinical evaluation becomes a general obligation of the

manufacturers according to the provisions of the Article 61 and Annex XIV, here including a post-market clinical follow-up (PMCF) [Article 10(3)] [13]. Moreover, MDR Article 2(38) provides the definition of the “lay person” as “the individual who does not have formal education in a relevant field of healthcare or medical discipline”.

Other considerations include the “clinical investigation” referred as a “systematic investigation” carrying out one or more subjects” to assess the guidelines for “safety and performance” of a device [Article 2(45)]. Notably, Article 71(3) suggests an increased need for the MS to assess whether the CI is designed considering the potential risks to subjects and third person after “risk minimization”. Also, the MDR sets out that the remaining risks are justified while considering “the clinical benefits to be expected”.

Another aspect involved in the MDR’s regulatory framework defines the “clinical data” as the “information concerning safety and performance” [Article 2(48)]. Therefore, the specification of these concrete purposes is in accordance with the stated sources of such data: (i) the CIs; (ii) other studies of the scientific literature; (iii) the reports issued by the scientific literature; (iv) other clinical relevant information “coming from the post-market surveillance”, in particular PMCF.

A comprehensive analysis of the MDR also reviews the definitions for: “subject” defined as “an individual” participating in a CI [Article 2(50)] and “informed consent” defined as a “free and voluntary expression” of the subject to participate in a specific CI [Article 2(55)]. The same article establishes the regulatory elements of the subject’s willingness “to participate” in a CI after having been “informed of all aspects” of the CI by linking the subject’s willingness and the approval to participate in a CI. The above definition suggests that the informed consent “shall be written, dated and assigned by the person performing the interview” [Article 63(1)]. In the CIs on minors (Article 65) and the CIs on incapacitated subjects (Article 64), the MDR requires “the informed consent” of the legally designed representative and the “explicit wish” of the subject “who is capable of forming an opinion” [Article 64(c) and Article 65(c)]. The ethical approach in these cases enables the assessment “to refuse participation” in a CI “or to withdraw” from a CI “at any time” [Article 64(c) and Article 65(c)].

Regarding the “clinical evidence”, the legal device of the MDR includes the clinical data and the clinical evaluation results “pertaining to a device of a sufficient amount and quality” in order to ensure a “qualified assessment” of the safety of the device with “intended clinical benefit(s)” [Article 2(51)].

A review of the MDR’s definitions focuses the regulatory challenges concerning the “clinical benefit”, the “adverse event”, and “the serious adverse event”. To address the definition of the “clinical benefit”, the MDR explores “the positive impact of a device on the health of an individual” here including “a meaningful, measurable, patient-relevant clinical outcome(s)” also related to “diagnosis” [Article 2(53)]. Meanwhile, Articles 2(57) and 2(58) provide an overview of the “adverse event” and “serious adverse event” discussing various factors and events in identifying “any untoward medical occur-

rence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding” [Article 2(57)] or “death”, “serious deterioration in the health of the subject”, “foetal distress”, “foetal death”, “congenital physical or mental impairment or birth defect” [Article 2(58)].

Furthermore, to meet the ethical guidelines and societal needs, the MDR enables the definition of the “ethics committee” set out as an “independent body” established in each Member State in accordance with the national law. The new regulation on MDs also assesses the views and opinions of the “patients or patients’ organisations” in the Article 2(55) and Article 62(3), with the aim to “contribute to the attainment of the highest standards of health for individuals” [14]. Recital 65 of the MDR focuses on the priorities of the MS where the CI is conducted to point the “appropriate authority to be involved in the assessment of the application to conduct” a CI. Admittedly, a very important definition at this point is the definition of the “investigator” meaning the “individual responsible for the conduct” of a CI [Article 2(54)]. The ethical approach of the MDR also assigns for the “investigator” the “individual” responsibility “at the clinical site” [Article 2(54)].

☞ Ethical principles in CIs

The MDR 2017/785 develops a transparent recognition of the key ethical requirements of the CIs [15]. Under the terms of the Annex XV, each phase of the CI, “from the initial consideration of need for and justification of the study to the publication of the result” is governed by the “recognized ethical principles” (Annex XV MDR 2017/785). Moreover, the new legal provision details: (i) the ethical approach to the CI report and the publication of the results of the CI; (ii) the ethical aspects and requirements of the summary of the CIP including the “monitoring and quality measures”; (iii) the ethical aspects regarding a CI “conducted in more than one Member State” (Recital 68); (iv) the ethical integrity of the CIs and the particular requirements regarding other CIs “not performed for any of the purposes listed in Article 62(1)” [Article 82(2)]; (v) the “statement of compliance” in accordance with “the recognized ethical principles for medical research” and “the principles of good clinical practice in the field of clinical investigations of devices” within the framework of the CIP “involving humans” (Annex XV).

Accordingly, the MDR outlines the ethical fundamentals of the medical research focusing new conceptual issues and guidelines with relevance for the human subject: “human dignity” [Recital 89 and Article 62(3)]; “integrity of the person” (Recital 89), “confidentiality” (Article 109), “protection of personal data” or “data protection” [Recital 67, Article 33(6)(9), Article 72(3)(4), Article 110 and Annex XV], “freedom of art and science” (Recital 89), “informed consent” [Article 2(55), Article 62(4), Articles 63–69], “right to property” (Recital 89).

In the light of the recent MDR, the ethical principles are discussed within the framework of the most recent version of the *World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects* (Recital 64) and the international standard

ISO 14155:2011 for CIs of MDs for human subject enabling “good clinical practice” (Recital 64).

Driven by the ethical principles, the patient healthcare and the population monitoring [16]; the recent literature argues few comments and discussions involving: the communication with the patient [17] and the ethical challenges of the medical research [18]; the smart technologies and patient safety [19]; the monitoring apps [8] and the high-risk MDs [20]; the biomedical knowledge and research [21, 22]; the MDs software and industry [23]; the medicine development and robotics [24]; the studies on artificial intelligence and medical innovation [25]; the ethical governance and the regulatory legislation in the EU [26]; the informed consent of the subject in case reports [27]; the ethics of withdrawal [28].

☞ Clinical evaluation and clinical investigation

The conceptual and methodological framework for the clinical evaluation and CI is developed by highlighting: (i) “the confirmation of conformity” in accordance with the safety and performance considering the “intended use” of the MD [Article 61(1)] and (ii) the need to base the clinical evaluation on a critical review of the recent literature regarding the safety [Article 61(3)(a)], the performance of the MD and a critical evaluation of “all available” CIs [Article 61(3)(b)]. Simultaneously, the MDR explicitly fixes the “general requirements regarding CIs conducted to demonstrate conformity of devices” (Article 62). In addition to this, the MDR establishes the equilibrium between the design and the conduct of the CIs reflecting the protection of “the rights, safety, dignity and well-being of the subjects” as participants in CI. The first part of the Article 62(3) displays, aside from the conceptual understandings, the enforcement of the clinical data “generated” as “valid, reliable and robust”. Regarding the conditions of the CIs, the MDR has the potential to fix a few ethical elements using the approach to: (i) the ethics committee established in accordance with the national law that “has not issued a negative opinion in relation to the clinical investigation” [Article 62(4)(b)]; (ii) the protection of “vulnerable populations and subjects” [Article 62(4)(d)]; (iii) the scrutiny of “the anticipated benefits” expressed as the central element to the subjects and public health justifying “the risks and inconveniences and compliance with this condition” [Article 62(4)(e)]; (iv) the informed consent of the subject or the legally designed representative [Article 62(4)(f)]; (v) the contact details provided to the subjects or the legally designed representative for an entity where additional information are provided “in case of need” [Article 62(4)(g)]; (vi) the safeguard of the right to physical and mental integrity and the protection of the data [Article 62(4)(h)]; (vii) the moral grounds of the CI that has to be designed “to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects” [Article 62(4)(i)]; (viii) the specification and the monitoring of “the risk threshold and the degree of distress” designed in the CIP [Article 62(4)(i)]; (ix) no improper influence on the subject or on his or her legally designed representative “to participate in the clinical investigation” [Article 62(4)(k)]; (x) the protection of

health and safety of the subjects here including, when necessary, “technical and biological safety testing and pre-clinical evaluation” [Article 62(4)(1)]; (xi) the respect of the general requirements (ethical principles and methods) and the documentation for the application for CI (application form and CIP) exposed in Annex XV.

☒ Informed consent in CIs

The recently issued MDR 2017/785 defines the “informed consent” as “a subject’s free and voluntary expression of his or her willingness to participate in a particular clinical investigation” [MDR Article 2(55)]. The same definition highlights the patient protection associating several articles with this regard: general requirements regarding CIs (Article 62); the informed consent (Article 63); the CIs on incapacitated subjects (Article 64); the CIs on minors (Article 65); the CIs on pregnant or breastfeeding women (Article 66); the additional national measures (Article 67); the CIs in emergency situations (Article 68) and the damage compensation (Article 69). Practically, the MDR legal provision focuses “a high level of protection of health of patients and users” (Recital 2), “patient needs” (Recital 30), “safety protection” and “citizens’ confidence” (Recital 50), “patient information” (Annex XV). This concerns, in particular, the main objective of the MDR “to satisfy individual patient interest” rather than the “interest of the community” [15]. However, the MDR provides the obligation for the informed consent to be “written, dated and signed” by the subject or the “legally designed representative” according to Article 63(1). The same article sets the terms of the informed consent provided by the person performing the interview “with a member of the investigation team” within the framework of the paragraph 2, point (c) under the provisions of the national law.

Practically, the “informed consent” is described by enabling the following information to the subject or his or her legally designed representative: (i) “the nature, objective, benefits, implications, risks and inconveniences” of the CIs [Article 63(2)(a)(i)]; (ii) the issue of the rights and guarantees regarding the subject’s protection [Article 63(2)(a)(ii)]; (iii) the right to withdraw from the CI of the subjects “at any time without any resulting detriment” and without “any justification” [Article 63(2)(a)(ii)]; (iv) the framework of a “comprehensive, concise, clear” and “understandable” information provided to the subject [Article 63(2)(b)]; (v) the information regarding the “applicable damage compensation system” [Article 63(2)(d)]. It is also important to note that the regulation requires “a clinical investigation report and a summary presented in terms understandable to the intended user” [Article 63(6) available in the electronic system on CIs as described in the Article 73 of the MDR]. Moreover, the European Commission will enable the interoperability for the electronic system stated by the Article 73(1) with the EU database for clinical trials on medical products for human use according to the Article 81 of the Regulation (EU) No. 536/2014 [29].

A particular emphasis of the MDR focuses on the issue of the CIs on the incapacitated subjects (Article 64), the CIs on minors (Article 65) and the CIs on pregnant

or breastfeeding women (Article 66). The regulatory framework of the “informed consent” subsequently targets additional measures to be maintained by the MS “regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical investigations, or persons in residential care institutions” (Article 67).

While the informed consent provides clear, concise and transparent regulatory framework, it also regulates the emergency situations (MDR Article 68). The following are some of the regulatory aspects with concise ethical implications: the informed consent to be involved in the CI is considered “at the time of the first intervention on the subject” [Article 68(1)] and the accordance with the CIP for that CI [Article 68(1)]. A comprehensive assessment of the conditions of the “informed consent” in emergency situations derives from the fulfillment of the following conditions: (i) the urgency of the situation [Article 68(1)(a)]; (ii) the subject “is unable to provide prior informed consent” and “to receive prior information” on the CI [Article 68(1)(a)]; (iii) the requirement of a “direct clinically relevant benefit for the subject” with the aim to improve the health [Article 68(1)(b)]; (iv) the need for the investigator to certify the unawareness of “any objections” previously emphasized by the subject regarding its participation in the CI [Article 68(1)(d)]; (v) the requirement for the CI to directly relate to the medical conditions of the subject [Article 68(1)(e)]; (vi) the CI “is conducted exclusively in emergency situations” [Article 68(1)(e)]; (vii) the entire CI involves “a minimal risk” and “minimal burden” while considering “standard treatment of the subject’s condition” [Article 68(1)(f)].

Recently, the scholarly literature raised comments and discussions regarding the ethical guidelines of the “informed consent”; the confidentiality within the clinical research [30–32]; the alternate views approaches in comparative effective research to “informed consent” when treatments compared are “non-investigational and low risk” [33] and the ethical approach to the rules for processing genetic, biometric and health data in accordance within the *General Data Protection Regulation* [34]. Other ethical issues discuss the clinical data requirements relating MDR and *In Vitro Diagnostic Medical Regulation* [35] and pointing: (1) the role of the Eudamed and its electronic system to raise transparency and to enable the public “to be adequately informed about devices” [Article 33(1)]; (2) the establishment of the Eudamed gathering: economic operators, Conformité Européenne (CE) Certificates of Conformity, CIs, the Unique Device Identification (UDI) database, the post-market surveillance [MDR Article 33(2)]; (3) the compatibility of the Eudamed “with the national databases and national web-interfaces to allow for import and export of data” [MDR Article 33(3)].

☒ Ethics committees in CIs

To enable the ethical and scientific requirements, the new regulatory framework also sets out corresponding legal provisions regarding the ethics committees within the “assessment of the application for authorization of a clinical investigation” [Article 62(3)] and in accordance

with the national legislation [Article 62(4)(a)]. In addition, the MDR is developing legal guidelines to assess the following conditions: (i) the requirement for the ethics committees not to issue “a negative opinion in relation to the clinical investigation”; (ii) the validity of the opinion is recognized for the entire Member State under the legal provisions of the national legislation [Article 62(4)(b)]; (iii) the requirements for the ethics committees to be involved in “the timelines for the authorisation” of the CI under the legal settings of the MDR (Recital 65).

From the legal and functional point of view, the ethics committee is “an independent body” [Article 2(56)]. However, the MDR offers a few requisites with concise ethical considerations: (i) the establishment of the ethics committees in a Member State is “in accordance with the national law; (ii) the requirement for the ethics committee to provide opinions in accordance with the aims and objective of the MDR; (iii) the need to take into account “the view of the laypersons”, especially patients or patients’ organizations (Recital 65).

☒ Conclusions

The MDR aims for harmonized implementation across the MS of the MDs regulation, which will enhance the protection of patients and users. The Regulation will also ensure high standards “of quality and safety for medical devices” and “a smooth functioning” of the EU internal market (Recital 2). However, the MDR has the role to set a clear regulatory framework as regards MDs that will positively serve the medical research by assessing the accountability and the statement of compliance with the ethical rules. In addition, the MDR concretizes an ethical-based approach of the informed consent referring to the “free and voluntary expression” of willingness regarding the participation in a CI. At the same time, one of the most challenging of the MDR’s legal requirements are those in which the Regulation revisits the concept of “medical device” to ensure the extension of the definition to all devices involved in the prediction and/or prognosis of diseases [Article 2(1)]. Finally, the MDR opens new paths for further researches assigning the clinical benefits to patients and the clinical safety of the devices.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper. All authors read and approved the final manuscript.

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