

# Eudamed's delay and its impact on disclosure of clinical investigations under the EU MDR

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## Abstract

The new European Database on Medical Devices (Eudamed) is the platform to be used for the prospective registration of clinical investigations for medical devices under the Medical Device Regulations. However, Eudamed's launch has been delayed till 2022. This article discusses the ramifications and the potential solutions for manufacturers to comply with public disclosure expectations and requirements. Until Eudamed is available, posting on other databases is recommended so manufacturers can meet requirements for clinical investigation transparency and disclosure while sharing clinical investigation information necessary to maintain public trust.

## Introduction

Under the new EU Medical Devices Regulation (MDR) 2017/745, there is an increased requirement to conduct clinical trials (clinical investigations) on certain risk classes of medical devices (Article 62).<sup>1</sup> Conducting clinical investigations also requires transparency and public disclosure of key information and documents.

The key factor in all these public disclosure activities is a fully functional new European

Database on Medical Devices (Eudamed) (Article 73), an electronic database that through its different, yet interoperable modules "will function as a registration system, a collaborative system, a notification system and a dissemination system (open to the public)".<sup>2</sup>

Under the EU MDR, the Eudamed module for clinical investigations will be publicly accessible.<sup>2</sup> The new Eudamed and all its modules were intended to replace the existing Eudamed and planned to be available well in time for the EU MDR date of application (DoA) on May 26, 2020. However, by late 2019, it was

announced that Eudamed will be delayed for at least 2 more years.<sup>2</sup> In March 2020, the European Commission postponed the EU MDR DoA for 1 year due to the COVID-19 pandemic.

## Clinical investigations disclosure requirements under the EU MDR

As defined in Article 73,<sup>1</sup> the registration of clinical investigations and the publication of their results must be on a publicly accessible electronic system as

**Table 1. Disclosure requirements for clinical investigations under the MDR**

Disclosure requirement	Provisions and location in the EU MDR 2017/745 <sup>1</sup>
<b>1. Clinical investigation registration</b>	<ul style="list-style-type: none"><li>• A clinical investigation must be registered in the electronic system for clinical investigations within the Eudamed (Article 73, 1).</li><li>• A unique ID number is assigned for each investigation (Article 70, 1; Article 73, 1a).</li><li>• This information is publicly accessible via Eudamed (Article 73, 3).</li></ul>
<b>2. Clinical investigation application documents</b>	<p>The following documents (Annex XV) must be submitted in the electronic system for clinical investigations within the Eudamed:</p> <ul style="list-style-type: none"><li>• Clinical Investigation Application: Annex XV, Chapter II, 1</li><li>• Clinical Investigation Plan (CIP): Annex XV, Chapter II, 3</li><li>• Investigator's Brochure (IB): Annex XV, Chapter II, 2</li><li>• CIP must describe policy on the publication of results (Annex XV, Chapter II, 3.17).</li><li>• This information is potentially publicly accessible via Eudamed (Article 73, 3).</li></ul>
<b>3. Clinical investigation results reporting and publication</b>	<ul style="list-style-type: none"><li>• A Clinical Investigation Report (CIR) will be prepared within 1 year of the end of the clinical investigation or within 3 months of the early termination or temporary halt, irrespective of the outcome (Article 77, 5).</li><li>• The CIR is accompanied by a summary easily understandable by the intended user (Article 77, 5).</li><li>• Publication of results should be according to legal requirements and recognised ethical principles (Annex XV, Chapter II, 3.17).<ul style="list-style-type: none"><li>• Declaration of Helsinki latest version (Preamble 64)</li><li>• ISO 14155:2011 (Preamble 64), replaced by ISO 14155:2020</li></ul></li><li>• This information is publicly accessible via Eudamed (Article 73, 3).</li></ul>

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part of Eudamed. Table 1 describes these requirements in more detail.

Interestingly, the EU MDR seemed to have anticipated the Eudamed delay under Article 123d:

Until Eudamed is fully functional, the corresponding provisions of Directives 90/385/EEC [Active Implantable Medical Device Directive (AIMDD)] and 93/42/EEC [Medical Device Directive (MDD)] shall continue to apply for the purpose of meeting the obligations laid down in the provisions listed in the first paragraph of this point regarding exchange of information including, and in particular, information regarding vigilance reporting, clinical investigations, registration of devices and economic operators, and certificate notifications.<sup>1</sup>

In the current regulatory setting, what do these delays mean for clinical investigation disclosure requirements? To answer this question, it is helpful to look at some lessons from the pharmaceutical industry.

### Impact of the Eudamed delay

This is not the first time that an EU electronic system has been delayed. The EU Clinical Trials Regulation 536/2014 (EU CTR)<sup>3</sup> entered into force in June 2014. However, the timing of its application also was dependent on having a fully functional EU clinical trials portal and database (collectively known as Clinical Trial Information System [CTIS], the pharmaceutical equivalent to Eudamed) to eventually replace the existing EU Clinical Trials Register and EudraVigilance database. The initial timeframe of the system’s launch was for December 2015. As of September

2020, the CTIS is still not functional and the earliest “go-live” date is planned for 2022.<sup>4</sup>

Like the EU MDR, the CTR has contingency measures to use provisions in the previous legislation, the Directive 2001/20/EC. Currently, the existing EU Clinical Trials Register continues to be used for prospective registration and posting clinical trials results.

Can the same approach be used for medical devices to meet requirement 1 listed in Table 1? The answer is no.

Unlike the existing EU Clinical Trials Register, the existing medical device database under both the MDD and the AIMDD is not designed for clinical investigation disclosure requirements. In its current form, “it is a central repository for information on market surveillance exchanged between national competent authorities and the Commission. Its use is



restricted to national competent authorities, it is not open for consultation and is not publicly accessible.”<sup>2</sup>

Without a fully functional new Eudamed, there are two options for clinical investigation sponsors to resolve the situation:

1. The clinical investigation is prospectively registered in another, existing clinical trial registry, such as one of those listed in the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP).<sup>5</sup>
2. Registration is deferred until the Eudamed is available (retrospective registration).

The current approach among device manufacturers is to proactively prepare all Eudamed requirements, not only those on clinical investigations, which will then be uploaded retrospectively once the Eudamed is operational. However, option 2 does not meet the requirement for prospective registration of clinical study information in the healthcare sector established over the years.

## Why prospective registration of clinical investigations should not be deferred

Transparency in clinical trials is not a novel requirement in the healthcare sector. While transparency began as a voluntary process, over the years it has evolved into a mandatory requirement. However, the European medical device industry has lagged behind in transparency due to a “fragmented” market approval process much different from that of medicinal products.<sup>6,7</sup> The EU MDR aims to change this.

Outside of the MDR, other legislations and guidance documents (as listed below) require clinical investigation disclosure. This forms a sound reasoning as to why manufacturers should consider option 1 to prospectively register their clinical investigations using existing registries.

### Requirements of EU member states

According to EU MDR Article 123d, until there is a fully functional Eudamed, the provisions on clinical investigations under the MDD and



AIMDD continue to apply, such as clinical investigation application and approval and reporting results that follow the requirements of each member state. Unfortunately, these member state requirements are not harmonised across the EU. At a minimum, each member state requires a unique study ID and registration on a public site. The preferred registration platform can vary. See currently available public clinical trial registries below.

### Declaration of Helsinki

The EU MDR refers to the “most recent version” of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The 2013 version states:

*Article 35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.*

*Article 36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.*<sup>8</sup>

### ISO 14155:2020

The ISO 14155:2020 Clinical Investigation of Medical Devices For Human Subjects – Good Clinical Practice standard was released in July 2020. One key addition to this new version is Section 5.4 Registration in publicly accessible database, which states “In accordance with the Declaration of Helsinki, a description of the

clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.”<sup>9</sup> It does not specify any preferred registry. The previous version of this ISO standard is cited as a recognized ethical guidance by the EU MDR (Preamble 64).

### International Committee of Medical Journal Editors (ICMJE)

The EU MDR refers to a need for a clear policy for publishing investigation results, placing an increased emphasis on the use of literature data as part of a manufacturer's clinical evaluation process. To publish in reputable biomedical journals, device manufacturers or sponsors must consider the ICMJE's Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.<sup>10</sup> Updated in December 2019, this guidance document requires preregistration of a clinical study in a registry that is a primary register or a data provider of the WHO ICTRP. Approval to conduct a study by a local, regional or national review body is not considered replacement for this prospective registration requirement. In addition, any manuscript based on clinical investigations must be accompanied by a data-sharing statement describing when and how the sponsor should share study documents (e.g., CIP, statistical analysis plan) and datasets (e.g., CIR).

## Currently available public clinical trial registries

In the absence of an operational Eudamed, there are several publicly accessible registries sponsors can use, including those that are part of the WHO ICTRP. Some of these are described below.

### ClinicalTrials.gov

Although not a primary WHO registry, the site is recognized as a WHO data provider. It is by far the largest clinical trial registry globally and covers drugs, biologics, surgical procedures and devices.

### European Clinical Trial Register

This is a primary WHO registry covering interventional clinical trials on medicines. It does not provide information on clinical trials for medical devices and procedures. However, it



does not preclude sponsors of devices, especially those of drug-device combination products, from using this platform for clinical investigation registration.

### Country-specific registries

Two EU countries have country-specific registries as part of the WHO ICTRP, Germany and the Netherlands. Neither registry distinguishes between trials on medicinal products and those on medical devices. They do cross reference to the ICMJE guidance document described above. However, it is important that sponsors and manufacturers consult the national competent authorities in the relevant Member State regarding their preferred register, if any.

### What comes after registration?

Registration of the clinical investigation protocol is the first step. The sponsor also needs to update information in the registry in case of changes and amendments and post results once the investigation is completed. The timing to post investigation results depends on the register and, in the EU, it is generally 1 year after the end of the investigation for adult subjects. The end of an investigation is defined as the date of the last visit of the last subject enrolled in the investigation (Article 77, 2).

Under the MDR, disclosure of results consists of making publicly available the CIR and the lay summary (requirement 3 in Table 1; Article 77, 5) through the Eudamed. It is also possible that other documents such as the CIP and IB (requirement 2) will be disclosed.

It is necessary to keep in mind that any information, data, or document posted publicly, regardless of the register, database or electronic system used, must comply with the requirements for personal data protection under the EU’s General Data Protection Regulation. Hence, the CIR and other documents should be written with data privacy in mind to ensure it is disclosure ready when the Eudamed is ready.

### Conclusion

Eudamed’s delay affects many EU MDR activities. The processes surrounding clinical investigations are especially important for novel and high-risk class devices where generation of clinical data is required. Other guidance documents, including those referenced in the EU MDR, require prospective registration and

posting the results of clinical investigations. Manufacturers will benefit from proactively fulfilling the requirements of clinical investigation transparency and disclosure as data sharing will help maintain public trust in the medical device industry. In addition, data submitted to existing clinical trial registries can easily be reused for Eudamed purposes in 2022.

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### Disclaimers

The opinions expressed in this article are the author’s own and not necessarily shared by her employer or EMWA.

### Conflicts of interest

The author is employed in the pharmaceutical industry.

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