

Analysis of Impact of European Medical Device Regulation and Brexit on the Regulatory Approaches in a Clinical Investigation Study on a New Class III Medical Devices Conducted in Europe and United Kingdom

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Keywords: Clinical Investigation, Regulatory Approach, Medical Device, CE Marking, European Medical Device Regulation 2017/745, Brexit, Ethics Committee, Competent Authority, High-risk Device.


Abstract: The evolution of technological innovations and medical devices requires particular reflections in terms of regulation. In order to harmonise practices between European countries and to reinforce clinical investigations, the European Regulation on medical devices 2017/745 has come to give a regulatory framework to the world of devices. A summary of the regulatory approaches for a clinical investigation of a new class III device conducted in France, Ireland and England is proposed in this article to illustrate the complexity of the processes, ending with an example. This illustrates the impact of the EU regulation and Brexit on the conduct of clinical investigations.


1 INTRODUCTION


Clinical investigations conducted in Europe were regulated until the end of May 2021 by the Directive 90/385/EEC on active implantable medical devices (EUR-lex, 1990) and the Directive 93/42/EEC on medical devices (EUR-lex, 1993). Each European country could thus transpose the directives into its national law, as for example France with the Jardé law (Legifrance, 2016), which separated research into three categories according to the risks incurred for the persons participating in this research.


The year 2021 is a year of major regulatory change, including the European medical device regulation and Brexit. The implementation of the European regulation on medical devices 2017/745 (EUR-lex, 2017) has thus aimed to harmonise practices between European countries. During 2021, the United Kingdom (UK) separates from the European Union (EU), known as Brexit, so that all European laws and regulations no longer apply in the UK, including the new European Medical Device Regulation.


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Here, we present the impact of these changes on the preparation and regulatory submission of a clinical investigation of a new class III medical device.

2 MEDICAL DEVICE REGULATION 2017/745

The European Medical Device Regulation 2017/745 (EU MDR) entered into force on 26 May 2021 after a year of delay due to the Covid crisis (EUR-lex, 2017). The EU MDR replaces Directives 90/385/EEC and 93/42/EEC on active implantable medical devices and medical devices respectively. A regulation, unlike a directive, is not transposed into the national regulations of each country; the Member States must apply it in full and directly. The regulation therefore aims to harmonise practices within Europe.

This EU MDR aims to strengthen market surveillance and the clinical evaluation process, to improve transparency through the European Database on Medical Devices (Eudamed) (<https://ec.europa.eu/tools/eudamed/>) and the unique device identifier (UDI), and to strengthen the quality and missions of notified bodies.

Manufacturers in order to market their device must obtain the CE marking. CE marking (figure1) is a guarantee that the product meets the essential safety and performance European requirements.



Figure 1: CE marking.

The manufacturer must therefore provide evidence of conformity with the requirements in accordance with Article 5 of the EU MDR: "The demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation as provided for in Article 61".

The purpose of this clinical evaluation is to collect clinical data on the medical device in order to verify, under normal conditions of use, that its performance corresponds to that claimed, to identify any undesirable side effects and to assess the risks for the patient.

Manufacturers, in order to demonstrate compliance with the essential requirements, must

plan, perform and document a clinical evaluation of the medical device. The clinical evaluation may be based on:

- a critical evaluation of scientific publications on equivalent devices
- a critical evaluation of the results of clinical investigations
- and the consideration of currently available alternatives

EU MDR specifies that, in the case of implantable devices and Class III devices, clinical investigations (CI) must be conducted. However, manufacturers are not required to conduct a clinical investigation if the following three criteria are met:

- the device has been designed by modifying a device already marketed by the same manufacturer
- equivalence with that device is demonstrated and approved by a Notified Body
- the clinical evaluation of the device currently marketed is sufficient to demonstrate compliance of the modified device with the relevant safety and performance requirements.

In the case of a brand new class III product without equivalent on the EU market, clinical investigation is required for its marketing in all European countries.

3 BREXIT AND CLINICAL INVESTIGATION

The United Kingdom (England, Scotland, Wales and Northern Ireland) withdrew from the EU on 1 February 2020. The withdrawal agreement (EUR-lex, 2019) between the EU and the UK provided for a transition period until 31 December 2020. The UK is thus considered a "third country" by the EU as of 1 January 2021.

3.1 Regulation of Medical Device and Clinical Investigation

Although the Medical Devices Regulation 2017/745 was written and came into force in 2017 when the UK was still part of the European Union, medical devices and clinical investigations in UK are not covered by this EU regulation anymore. Medical devices remain regulated by the UK Medical Device Regulation 2002 (Legislation.gov.uk, 2002). This regulation is the adaptation of the European Directive 90/385/EEC and the European Directive 93/42/EEC into UK law.

3.2 The CE Mark and UKCA Mark in UK

Following the UK's separation from the European Union, the CE mark, which guarantees the conformity of devices to the essential performance and safety requirements of the EU, is no longer applicable to medical devices in the UK. Medical devices must now be UKCA (UK Conformity Assessed) certified in order to move freely in the UK. There is a transition period for CE marked devices to be recognised in the UK until 1st January 2023, allowing manufacturers to build up the required dossiers for UKCA marking (figure 2). The UKCA marking is, in some ways, similar to the CE marking as the majority of UK standards follow the European standards. One of the main differences lies in the bodies responsible for issuing the UK or CE mark.



Figure 2: UKCA marking.

The UKCA certificate must be issued by approved Notified Bodies responsible for assessing the conformity of the device with UK requirements. The guide "UK approved bodies for medical devices" listing the notified bodies is available on the UK government website (<https://www.gov.uk/government/publications/medical-devices-uk-approved-bodies/>).

UK-based notified bodies, which were competent to assess the conformity of European products and issue the CE certificate, are no longer recognised in the EU and therefore can no longer issue these CE mark certificates.

3.3 Data Protection

In the course of a clinical investigation, the personal and health data of participants are processed, collected and analysed for scientific research purposes. The sponsor, person or institution responsible for the implementation, management or financing of a clinical study is thus responsible for the protection and confidentiality of collection, transfer and treatment of personal data during the study.

The General Data Protection Regulation (GDPR) (EUR-lex, 2016) governs the processing of personal data and the rules on the free movement of personal data in Europe. The UK has special provisions regarding the GDPR. Thanks to the Trade and Cooperation Agreement (EUR-lex, 2021b) concluded on 24th December 2020, the GDPR remained in force throughout the UK until 1st July 2021. This meant that data transfer with the UK could take place under the terms of the GDPR until 1st July 2021 without it being considered a third country. After 1st July, if there was no European Commission decision authorising the transfer of personal data to the UK ("adequacy decision"), the country would have been listed as a third country for the transfer of data and the UK would have had to demonstrate that it had a sufficient and adequate level of data protection for transfers to continue. Instead, the European Commission adopted an adequacy decision on the UK and the General Data Protection Regulation on 28th June 2021 (EUR-lex, 2021a). The European Commission found, through its decisions, that the UK enjoys a level of protection substantially equivalent to that guaranteed by EU law and thus transfers of personal data from the EU to the UK could proceed without further specific directives.

4 REGULATORY APPROACHES FOR CLINICAL INVESTIGATION

In the EU MDR, clinical investigation is defined as "any systematic investigation involving one or more human participants to assess the safety or performance of a device". Clinical investigations are time-consuming and expensive studies with complex regulatory procedures.

4.1 Multinational Clinical Investigation

Multinational clinical investigations are investigations conducted with a common methodology in more than one country and a common recruitment pool across all participating countries. In this way, the multinational dimension allows access to a larger number of subjects and thus reduces the duration of the study and its cost while also improving generalisability of participant characteristics. It allows the device to be evaluated in different environments and so ensures that it is compatible with different organisations.

Finally, the results can be extrapolated more easily as the study is conducted in more

representative country and manufacturers benefit from better exposure of their product, which can facilitate its market penetration once it has been CE marked.

The main challenge of multinational studies is to apply for a clinical investigation authorisation from the regulatory authorities - ethics committee and competent authority. Although European projects are subject to the same regulations, these regulations leave some room for manoeuvre to national law. Moreover, evaluation of the study by the ethics committee is specific to each country and the procedures for submission to the competent authorities of each Member State are not harmonised between European countries as yet and until establishment of this function under the Eudamed platform.

4.2 Common Rules for Clinical Investigations

Clinical investigation, regardless of their size (monocentric, multicentre, international) and their purpose (compliance with essential requirements, post-marketing clinical follow-up, etc.), must be conducted in accordance with rules on ethics and good clinical practice.

4.2.1 Ethics Rules

A clinical investigation must be designed and conducted in an ethical manner. The first ethics principles were proclaimed in 1947 by the Nuremberg Code, which followed the crimes against humanity committed during the Second World War. This text was then completed by the Helsinki Declaration (World Medical Association, 2013) in 1964. These international texts now constitute the key principles of ethical research.

4.2.2 Conduct Rules

The clinical investigation should also be designed and conducted in accordance with good clinical practice. ICH Good Clinical Practice (GCP: ICH E6(R2)) is an international ethical and scientific quality standard for clinical trials involving human subjects (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016). This standard has its origin in the Declaration of Helsinki. GCP: ICH E6 describes a standard for the design, conduct, recording and reporting of clinical studies.

Recently, an expert group has established the ISO 14155 (International Organization for Standardization, 2020) standard which cites Good Clinical Practice specific to clinical investigations. This standard is based on ICH GCP E6: R2 and uses terminology more appropriate to medical devices. ISO 14155 has its origins in the Declaration of Helsinki, whose objective is to protect the rights, safety and well-being of subjects and to ensure that these principles prevail over the interests of science and society.

The ISO 14155 standard states in part that a clinical investigation:

- must be conducted under the responsibility of a sponsor and should be conducted at the research site by qualified investigators
- must be conducted in accordance with a clinical investigation plan (protocol)
- must have received the approval/favourable opinion of the local ethics committee
- must have received no objection from the local regulatory authorities (if applicable)
- the subject must have been adequately informed about their participation and the risks involved. The subject must have freely given consent before participating in the clinical investigation
- medical devices used in clinical investigations should be used in accordance with the investigator's brochure, the protocol and the instructions for use

4.2.3 Data Protection Rules

Clinical investigations conducted in the EU and United Kingdom must also comply with the GDPR. To ensure the protection of the rights and freedoms of individuals, technical and organisational measures must be taken.

The study sponsor must therefore ensure that the study complies with the GDPR, since health data, which is both personal data and sensitive data, is processed. The person must be informed about the processing of his data and give his consent to the processing of his data.

4.3 Regulation of Clinical Investigation in Europe

Clinical investigations are governed in Europe by the European Medical Devices Regulation 2017/745. The establishment of a common regulation as EU MDR is a real opportunity to harmonize the evaluation time but also to develop a system of vigilance of medical

devices, absent until now. Chapter VI of the EU MDR is entirely devoted to the regulation of clinical evaluations and clinical investigations.

For medical devices of class III, invasive and implantable device, the study must get the following requirements:

- validated by the Member State: it must ensure that the study falls within the scope of the EU MDR and that the application dossier is complete
- authorised by the Member State after a full assessment of the application file
- authorised by the Ethics Committee after evaluation of the dossier
- covered by insurance/indemnity in case of injury to participants due to their participation in the research
- any adverse events must be recorded and reported to the Member State
- carried out under the responsibility of a sponsor established in the UE

For clinical investigations of class I medical devices and class IIa and IIb non-invasive devices, the requirements are the same, except that the study does not require Member State authorisation. Article 70 paragraph 7a stipulates that clinical studies require only a validation from the Member state and the favourable opinion of the ethics committee unless otherwise stated by national law. French and Irish law make use of the opening clause in Article 70(7a) for clinical investigations with low risk medical devices.

Annex XV of MDR details documents to submit to member states for validation and/or authorisation by the member state. Each Member State may request the submission of specific documents to make its assessment. Files to submit to the ethics committee are dependent on the local committee.

The EU MDR specifies that the application for a clinical investigation must be submitted via the Eudamed and that the summary and results of the application must be filed on the portal. The clinical investigation module of the Eudamed electronic system is currently not available and will only be deployed from 2022 onwards, the application must be made according to national procedures during the transitional period according to the MDCG 2021-16 (Medical Devices Coordination Group, 2020).

4.3.1 Specific Country Regulation

We will present the specific regulation in three countries by detailing the regulatory authority with responsibility for the clinical investigation, the

documents required for submission and the evaluation timeframes: France, Ireland and England

France. The competent authority in France is the National Agency for Medicines and Health Products – ANSM (<https://ansm.sante.fr/>). It is in charge of authorising and monitoring clinical studies on medicines, medical devices, non-health products and cosmetics in France.

Ethics committee responsible for issuing an opinion on research projects in France is the “Comité de Protection des Personnes (CPP)”. There are 40 CPPs in France and the opinion of a single CPP is required at national level, regardless of the number of centres. The study files will be submitted on a national platform and the appointment of a CPP is done by drawing lots.

The requirements specific to the class of the device are summarised in the Table 1 and the difference from the EU MDR are indicated by (*), using of the opening clause in Article 70(7a).

Table 1: Regulatory procedures required in France to conduct a clinical investigation to establish the conformity of a medical device according to its class.

	ANSM validation	ANSM authorisation	CPP opinion
Class I	x		x
Class IIa non-invasive			
Class IIb non-invasive*	x	x	x
Class IIa and IIb invasive			
Class III			

Researchers and manufacturers can refer to the guide "Avis aux promoteurs - Investigations cliniques de dispositifs médicaux relevant du Règlement Européen N° 2017/745 Partie I" (ANSM, 2021) available on the ANSM website for the conduct of their clinical investigations.

To obtain authorisations from the regulatory authorities, the applicant must first obtain an IDR/CB registration number for its research and obtain the designation of a CPP. The complete application file must then be submitted to the designated CPP and to the ANSM on the same day but separately: by email or on the Eudralink platform for the ANSM (<https://eudralink.ema.europa.eu/>) and on the CNRIPH platform for the CPP (<https://cnriph.sante.gouv.fr/>).

The ANSM has 10 days to validate the application in accordance with the EU MDR. Then the ANSM and the CPP must give their opinion within 45 days. This period may be extended by 20 days by the ANSM if experts' consultation is needed.

Ireland. The Health Products Regulatory Authority – HPRA - (<http://www.hpra.ie/homepage/medical-devices>) is the regulatory authority for health products as medicines, medical devices, cosmetics for humans and animals in Ireland. The HPRA is the authority responsible for assessing and authorising clinical trials of medicines and medical devices.

The ethics committee in Ireland is the National Research Ethics Committee - NREC, a national ethics committee (<https://www.nrecoffice.ie/>).

The requirements specific to the class of the device are summarised in the Table 2 and the difference from the EU MDR are indicated by (*), using of the opening clause in Article 70(7a).

Table 2: Regulatory procedures required in Ireland to conduct a clinical investigation to establish the conformity of a medical device according to its class.

	HPRA validation	HPRA authorisation	NREC opinion
All class of devices*	*	x	x

The "Guide to Clinical Investigations Carried Out in Ireland"(HPRA, 2021a) is a reference for researchers and manufacturers.

The authorisation application to be submitted to the HPRA must be filed on the Common European Submission Portal (<https://cesportal.hma.eu/>). For the ethics committee, the file must be sent by email to the NREC.

The HPRA has a period of 45 calendar days to evaluate the application after validation of the file. The HPRA may consult experts and an additional 20 calendar days is added. The NREC meets once a month to assess applications. The investigator must submit the application 12 days before the date of the plenary meeting and receives a response within 55 days of meeting.

The sponsor must pay fees to the HPRA (HPRA, 2021b) and NREC (<https://www.nrecoffice.ie/apply-2/fees/>) for their initial evaluation of the application. NREC fees are function of industrial or academic lead and raised at 500€ and 75€ respectively. Fees for HPRA are dependant of the class of the device:

- class III and IIb medical devices or active implantable device: 4300€
- class IIa and class I medical devices: 1900€

In case of substantial amendment or resubmission, supplementary fees are required.

4.3.2 Regulation of Clinical Investigation in UK

The United Kingdom is a "third country" by the EU. The EU Medical Devices Regulation 2017/745

therefore does not apply to the UK and clinical investigations in the UK are governed by the UK Medical Devices Regulations 2002 (Legislation.gov.uk, 2002).

For a clinical investigation of all class of devices, the following requirements are needed:

- sponsor is established in UK or in a country listed in the EU and/or the European Economic Area.
- a favourable opinion from the ethics committee
- the authorisation of the competent authority
- the consent of each included subjects
- an insurance/indemnity in case of injury
- to report the adverse event

The competent authority in United Kingdom is the Medicines and Healthcare Products Regulatory Agency – MHRA (<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>). The MHRA is the body responsible for assessing and authorising applications for clinical investigations.

There are over 80 different Research Ethics Committees (RECs) in the UK within the Research Ethics Department of the UK Departments of Health (<https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/>). RECs are classified as "flagged RECs" according to the professional, academic and ethical expertise of the committee members. For clinical investigations, 10 flagged RECs are listed in England. Approval of only one REC is required, regardless of the number of centres involved in the clinical investigation.

The requirements specific to the class of the device are summarised in the Table 3.

Table 3: Regulatory procedures required in England to conduct a clinical investigation to establish the conformity of a medical device according to its class.

	MHRA authorisation	REC opinion
All class of devices	x	x

The application to the MHRA and the REC must be submitted on the Integrated Research Application System by the principal investigator of the research in England (<https://www.myresearchproject.org.uk/>). Where the clinical investigation involves the NHS, patients or NHS staff, approval from the HRA is required. This application is made in conjunction with the REC application. The MHRA and the REC each have 5 days to confirm receipt and completeness of the application after receipt and 60 days to assess the application.

The sponsor must pay a fee for the initial evaluation of the application by the MHRA (<https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees>), which depends on the class of the device:

- Group A includes Class I, IIa and IIb devices other than long-term implantable/invasive devices: £3820
- Group B includes Class IIb implantable/long term invasive, Class III, active implantable devices: £5040

In case of amendment or resubmission, supplementary fees are required by MHRA.

5 PRACTICAL EXAMPLE

The Selio project is a multi-partner European funded, project on the development of a new medical device which will be class III in Europe. This project is supported by EIT Health. It was born during the period of transition from the European Medical Device Directive to the European Medical Device Regulation and the separation of the UK from the European Union. The EU Medical Device Regulation 2017/745 and Brexit has directly affected the project and the regulatory steps required to obtain authorisations to start a clinical investigation involving French, Irish and English partners. We present here the expected flow chart of regulatory steps for the preparation and submission of a clinical investigation on a new class III medical device.

Class III medical device products without equivalent on the EU market, require a clinical investigation in the framework of the clinical evaluation. A Notified Body will then have to assess the conformity of the device with the European requirements in terms of safety and performance in order to issue the CE mark.

In order to reduce recruitment time and increase recognition of scientific value, one option for this project is to conduct a multinational clinical study with French, Irish and English centres. Science is stronger when it is collaborative. The UK has been one of the most important scientific partners in Europe for decades. Their lack of participation in such large-scale projects, due to policies different from those of Europe or regulatory procedures too complex to include them in such projects, would have an impact on the value of science.

For the conduct of this clinical investigation, the sponsor will have to prepare and submit an application for authorisation in each of the countries

participating in the study. He will thus have to prepare the documents required for the competent authorities and ethics committees for their evaluation of the study and their authorisation.

Although some of the documents are common - the clinical investigation plan, the information note and consent form, the investigator's brochure and the proof of insurance - the latter part of the documents is specific to each authority and thus requires additional time and regulatory expertise to draft.

The work required for a multinational study is much more time and resource intensive than a national study. It is necessary to have a regulatory contact in each of the countries participating in the study for the preparation of the regulatory procedures. The project team is composed of scientific experts, project managers, clinical research associates and clinical study technicians. In addition, an operational and scientific committee participates in the construction, validation and follow-up of the study.

The study can start in a given country once the competent authority has given its authorisation and the ethics committee has given a favourable opinion. In an ideal situation, which means without the need for the regulatory authorities to consult experts or issue comments and/or modifications to the research, the research could start approximately two months after the submission of the application in each country (table 4).

Table 4: Delay of assessment in days for competent authorities and ethics committee of France, Ireland and England. The delay indicated are minimal delay, i.e. without expert consultation or question to the sponsor.

	Competent authority	Ethics committee
France	55	55
Ireland	45 + x days for validation	55
England	65	65

In most cases, studies receives from regulatory authorities opinions subject to minor or major changes, which can extend the assessment period by up to 6 months. Furthermore, in the case of multinational studies, requests for changes to the study protocol must be carried over all countries in the form of amendments. This not only lengthens the evaluation periods but also leads to additional costs when the activities of the regulatory authorities are invoiced.

In accordance with the previously announced costs, the budget for the initial submission of a clinical study to the regulatory authorities can amount to more than 10,000€. The budget is consequent and should not be neglected during the financial set-up.

The variation in evaluation time and cost is significant when considering best and worst case scenarios. Investigators and project leaders need to be able to explain this to funders and investors.

6 WHAT ABOUT THE COORDINATED EVALUATION PROCEDURE WITH THE EU MDR AND THE EUDAMED PLATFORM?

A coordinated evaluation procedure for clinical investigations taking place in more than one Member State will be introduced with the establishment of the Eudamed, and this procedure will be made mandatory for European clinical investigations from 26 May 2027.

The coordinated evaluation procedure will thus simplify the sponsor's procedures, who will only have to submit one application for authorisation of a clinical investigation in Europe, regardless of the number of European countries participating in the study.

A coordinating Member State will be identified among the Member States participating in the clinical investigation. The coordinating Member State will be responsible for assessing whether the clinical investigation falls within the scope of the EU MDR, for verifying that the application is complete in accordance with Annex XV with the exception of certain documents which are subject to assessment by each Member State, and for issuing an assessment report. This report will have to be communicated to the Member States in order to obtain their comments on the project. The coordinating Member State will then have to issue a final evaluation report to the sponsor taking into account the comments of the Member States within 45 days of the validation of the application. This period may be extended to 95 days if the study concerns a class IIb or III DM and expert consultation is required.

7 CONCLUSION

Clinical investigations are long and costly studies. The regulatory approaches could be cumbersome,

even more in the context of a multinational study. The submission system to be used differ from one country to another, the documents expected by the regulatory authorities must be adapted to each regulatory authority in respect of their national regulations and the time period for the evaluation is also different and dependant of certain factors. One potential risk could be that investigators would seek to limit their study to one jurisdiction or leave the UK out, resulting in poor science and less confidence in the quality and applicability of the devices after authorisation.

Although the European regulation tends to harmonise practices for European countries, in the absence of the Eudamed platform, these remain complex and can therefore be a hindrance to conducting a study of this scale.

The main advice to be drawn from this example is that the sponsor should surround himself with people with appropriate regulatory expertise at the design stage of the project. For example identifying a regulatory contact in each of the countries involved in the study, which will enable him to be informed of the regulatory steps to be taken for his clinical investigation: the documents to be prepared, the authorities in charge of the evaluation and the deadlines to be respected.

The time needed for the assessment of the study by the regulatory authorities should not be neglected when planning the study (best or worst case scenario). This time, together with the preparation of regulatory documents, can sometimes exceed one year, especially in projects of this size. It should therefore be anticipated for smart project management.

In Europe, project sponsors of multinational clinical trials can also be supported by the European Clinical Research Infrastructure Network (ECRIN), which can conduct by delegation some sponsor tasks (<https://ecrin.org/>).

ACKNOWLEDGMENTS

The Selio project has received funding from the EIT Health (<https://eithealth.eu/>): ID 20186.

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