Guidance for Application/Notification for Clinical Investigations under Regulation (EU) 2017/745 on Medical Devices

1. Introduction

The guidance described in this document is based on the principles outlined in the Medical Device Regulation (EU) 2017/745 (MDR), concerning Clinical Investigations in Articles 62 to 81 and Annex XV. This document is a guidance to the local form *MT-MDF15 Clinical Investigation – Application/Notification form under Regulation (EU) 2017/745*.

In order to obtain an authorisation from the Malta Medicines Authority, the sponsor, or its legal representative in cases where the sponsor is not established in the Union, shall submit an application to the Authority. The application should be accompanied by the request to the relevant Ethics Committee/s in Malta.

Before the submission of an application or notification, the Malta Medicines Authority strongly recommends that the applicant arranges a pre-submission meeting with the Authority, to discuss the clinical investigation and obtain further information from the Medical Devices review team on the requirements for authorisation. Reference should be made to *MT-MDF14 Application for Pre-Submission Meeting Request for Clinical Investigations/Performance Studies* and *GL-MDF17 Guidance for Application for Pre-Submission Meeting Request for Clinical Investigations/Performance Studies.*

If a sponsor intends to introduce modifications to an authorised clinical investigation, reference should be made to *GL-MDF15 Guidance for Notification for Modification of Clinical Investigations under the Regulation (EU) 2017/745*, available on the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

The mandatory use of the European databank platform as a registration system will start when the entire EUDAMED modules have been declared fully functional, in accordance with Article 73 of the Medical Device Regulation.

2. Scope

This document has been prepared to guide applicants when submitting forms related to clinical investigations to be carried out in Malta, to ensure that Medical Devices Regulation requirements and expectations are fulfilled.

The sponsor is encouraged to refer to the latest version of International Standard ISO 14155:2020 – Clinical investigation of medical devices for human subjects.

3. Terms, Definitions & Abbreviations

Authorised Representative
Authorised representative means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation. [Regulation (EU) 2017/745 Article 2(32)]

Clinical Investigation
A clinical investigation is defined as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device. [Regulation (EU) 2017/745 Article 2(45)]

Ethics Committee
Ethics committee means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of the Medical Devices Regulation, taking into account the views of laypersons, in particular patients or patients' organisations. [Regulation (EU) 2017/745 Article 2(56)]

Ethics Committee/s in Malta
Health Ethics Committee; Research Ethics Committee.

Legal Representative
Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to the MDR and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor. [Regulation (EU) 2017/745 Article 62(2)]

Manufacturer
Manufacturer means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark. [Regulation (EU) 2017/745 Article 2(30)]

Medical Device
A medical device is any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:
- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:
- devices for the control or support of conception,
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) of the Medical Device Regulation (medical devices, accessories for medical devices, and products listed in Annex XVI) and of those referred to in the first paragraph of this point. [Regulation (EU) 2017/745 Article 2(1)]

Sponsor
Sponsor means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation. [Regulation (EU) 2017/745 Article 2(49)]

Abbreviations

EUDAMED European Database on Medical Devices

MDCG Medical Device Coordination Group

MDR Medical Device Regulation referring to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC.

MMA Malta Medicines Authority

N/A Not applicable

PMCF Post-Market Clinical Follow-up

4.1 Types of clinical investigations

Different types of clinical investigations are subject to the respective requirements, relevant to the MDR, as described in Table 1. For all clinical investigations, the documentation submitted to the Malta Medicines Authority must be identical to the documentation sent to the Ethics Committee/s in Malta.

Reference is made to guidance documents:
- *MDCG 2021-08 Clinical investigation application/notification documents*
- *MDCG 2024-03 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices*
- *MDCG 2024-05 Guidance on content of the Investigator's Brochure for clinical investigations of medical devices*
- *MDCG 2021-06 Regulation (EU) 2017/745 Questions & Answers regarding clinical investigation*
- *MDCG 2024-05 Guidance on content of the Investigator's Brochure for clinical investigations of medical devices*
- *2023/C 163/06 Commission Guidance on the content and structure of the summary of the clinical investigation report*

Reference is also made to the Malta application form *MT-MDF15 Clinical Investigation – Application/Notification form under Regulation (EU) 2017/745*.

Type of clinical investigation	**Relevant MDR Articles & Annexes**	**EU Form**	**MMA Form**
Clinical investigations for Non-CE Marked Medical Devices	Article 62; Annex XV	Clinical investigation – application/notification form under the Medical Device Regulation as per MDCG 2021-08	MT-MDF15
Clinical investigations of a device bearing the CE marking, to be used outside its intended purpose	Article 74(2); Annex XV		
PMCF Investigations, where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use and these procedures are invasive or burdensome	Article 74(1); Annex XV		

Table 1: Clinical investigations regulatory pathways

4.2. Documentation required

For clinical investigations to be conducted in Malta, it is the responsibility of the sponsor of the clinical investigation to complete and submit all requested forms and supporting documentation to the Malta Medicines Authority, in accordance with Annex XV of the MDR and this document. The relevant EU and local forms for different types of clinical investigations are listed in Table 1.

4.3 General details related to Application

4.3.1 Application Form Title

The application form related to this guidance document is *MT-MDF15 – Clinical Investigation – Application/Notification form under Regulation (EU) 2017/745*, which may be accessed from the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

4.3.2 Application Format

MT-MDF15 Application Form is in a fillable pdf format. Form should be filled in electronically using the shaded areas. Handwritten forms may not be accepted if writing is considered illegible.
Forms should be signed and submitted as a scanned copy or as a signed pdf file.

4.3.3 Official Languages

The official languages in Malta are Maltese and English. All application forms and supporting documentation must be completed in either Maltese or English.

4.4 Filling in the Application Form

All sections must be completed. The application form is divided as follows:

- Section A – Application Introduction and Applicant Details
- Section B – Sponsor Contact Details
- Section C –Legal Representative Contact Details
- Section D – Manufacturer and Authorised Representative Contact Details
- Section E – Notified Body Contact Details
- Section F – Investigator Contact Details
- Section G – Application / Notification Form (EU)
- Section H – Details of Payment
- Section I – Data Protection Consent Statement
- Malta Medicines Authority Declaration for Form Submission

4.4.1 Section A: Application Introduction

Section A is divided into two sections:

Section A.1 Date of application and applicant contact details

The individual completing the application shall provide the following information: Date of the application, applicant's name, surname, email address and contact number.

Section A.2 Applicant

The applicant making the request, whether the sponsor or the Authorised Representative, must be selected. If the applicant is the sponsor, Section B must be filled in. If the applicant is the Legal Representative (when the Sponsor is outside the Union), section C must be filled in. It is the responsibility of the applicant to update the Authority of any changes in the details of the application.

4.4.2 Section B: Sponsor Contact Details

The details of the sponsor should be included in this section. If the organisation is registered with the Authority, quote the reference number.

4.4.3 Section C: Legal Representative Contact Details

A Legal Representative is required when the sponsor is located outside the Union. The details of the Legal Representative should be included in this section. If the organisation is registered with the Authority, quote the reference number.

4.4.4 Section D: Manufacturer and Authorised Representative Contact Details

The organisation making the request, whether the manufacturer or the Authorised Representative, must be selected. If the organisation is the manufacturer, section D.1 must be filled in. If the organisation is the Authorised Representative (when the manufacturer is located outside the Union), section D.2 must be filled in. Local organisations should be registered with the Authority and the reference number must be quoted in this section.

4.4.5 Section E: Notified Body Contact Details

The Identification Numbers of the Notified Body or Notified Bodies involved, are given in this section.

4.4.6 Section F: Investigator Contact Details

The contact details of the investigator are to be provided. The following information is requested: Name, telephone number, job title, email address and healthcare institution details.

4.4.7 Section G: Application / notification form (EU) including documents

The applicant is required to submit an application/notification to the Malta Medicines Authority, accompanied by the documentation referred to in Chapter II of Annex XV of the MDR.

For this section, refer to the *MDCG 2021-08 guidance Clinical investigation application/notification documents*. The attachments of this document provide the following templates, which must all be submitted:

- Clinical investigation – application/notification form under the Medical Device Regulation
- Clinical investigation supporting documents - Appendix of documents to be attached
- Checklist of general safety and performance requirements, standards, common specifications and scientific advice
- Acknowledged application request submitted to the Ethics Committee/s in Malta.

4.4.8 Section H: Details of payment

Reference should be made to the *GL-MDF07 Guidance on fees in relation to Medical Devices* available on the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

The applicant is requested to attach **Proof of Payment.** This document will be verified by the Finance & Corporate Services Unit at the Malta Medicines Authority, confirming receipt of funds.

4.4.9 Section I: Data Protection Consent Statement

Applicant shall confirm consent, by ticking the box in this section, to the processing of personal data by the Malta Medicines Authority and understands that this data shall be processed in accordance with the General Data Protection Regulation (GDPR).

4.4.10 Malta Medicines Authority Declaration for Form Submission

Applicant shall sign the Malta Medicines Authority declaration that all the information submitted within this application form is correct and complete.

4.5 Letter of Authorisation Validity

The start of a clinical investigation must take place within two years of the date of approval of your study.

4.6 Timeframes

Timeframes for the processing of applications are stipulated by the MDR. Refer to Table 2 for a summary of the timeframes required for the processing of the application by the Malta Medicines Authority and the timeframes for the sponsor to respond to the Malta Medicines Authority, should the Authority require any further information or clarification. Such requests shall be communicated to the applicant.

The clock is stopped when the applicant is requested to send additional information or comments and restarted upon receipt of responses and review resumes. If further queries arise or responses are not satisfactory, the applicant is informed and clock stops/starts accordingly, with the cycle repeating itself.

	Process Stage	**Responsibility**	**Timeframe**	**Extension of Timeframe**
Review Stages MDR - Article 62 & Article 74(2)	Review of application / notification form by MMA	MMA Reviewer	Reviewer to notify sponsor within 15 days of the receipt of the application	N/A
	Comments and/or additional information requested by MMA	Sponsor	Sponsor to reply within 10 days of the request for additional information / comments	Can be extended by a further period of 20 days
	Receipt of comments / additional information sent by the sponsor	MMA Reviewer	Reviewer to notify sponsor within 10 days of the receipt of request for comments / additional information	NA
Assessment Stage MDR - Article 70(7)b	Assessment of documentation within the application / notification by MMA	MMA Reviewer	Within 45 days of the review date	Can be extended by a further period of 20 days if experts need to be consulted

PMCF Investigation MDR - Article 74(1)	Review and assessment of the notification by MMA	MMA Reviewer	Within 30 days of commencement of the investigation.	N/A

Table 2: Timeframes stipulated by the MDR for the different stages in the processing of application form

4.7 Refusal of authorisation of a clinical investigation

The Malta Medicines Authority may refuse to authorise the initiation of the clinical investigation. The reasons for its rejection shall be provided to the sponsor via a written communication.

4.8 Initiation of a clinical investigation

Ethics committee approval is not mandatory before the application submission to the Malta Medicines Authority. The applicant must provide the Authority as per section 5.2.4, the acknowledged application request submitted to the Ethics Committee/s in Malta, as part of the documentation submitted with *MT-MDF15*. The clinical investigation can only commence once the sponsor receives the Letter of Authorisation from the Malta Medicines Authority by email. Before starting the clinical investigation, the sponsor should provide a positive decision of the Ethics Committee/s to the Malta Medicines Authority and should also notify the Authority of the commencement date. The description of the 'Commencement date' should be defined in the Clinical Investigation Plan.

4.9 End of a clinical investigation in Malta

The sponsor is expected to report to the Malta Medicines Authority the termination of the clinical investigation within 15 calendar days of the end the clinical investigation in Malta. If the clinical investigation is also conducted in other Member States, the sponsor shall also notify all the Member States in which it was conducted, when it has been completed in all the Member States. This notification shall be made within 15 days of the end of the clinical investigation in the last Member state. If the clinical investigation is still ongoing in one or more third countries when the end of the clinical investigation in the EU is reported, the sponsor should inform the concerned Member States of the expected end of study globally if this does not coincide with the end of study in the EU. Sponsors are encouraged to notify the Member States concerned to confirm the actual end of study globally, once reached.

In accordance with the MDR, the sponsor is responsible for submitting a Clinical Investigation Report within one year of the end of the clinical investigation, irrespective of the outcome. If the clinical investigation has been temporarily suspended or terminated early, the Clinical Investigation Report must be sent within 3 months, unless it is restarted within 3 months of the temporary halt. In such cases, the sponsor does not have to submit a clinical

investigation report until the clinical investigation has been completed. The final clinical investigation report should include details regarding the temporary halt.

4.10 Reporting of adverse events

Refer to *GL-MDC01 Guidance on reporting of adverse events in clinical investigations and performance studies.*

4.11 Contact details for further information

All filled in forms and accompanying documents should be submitted by email to mdforms.medicinesauthority@gov.mt

5. References

Malta Medicines Authority - Medical Devices
https://medicinesauthority.gov.mt/medicaldevices?l=1

GL-MDF07 Guidance on fees in relation to Medical Devices

GL-MDF15 Guidance for Notification for Modification of Clinical Investigations under the Regulation (EU) 2017/745

GL-MDF17 Guidance for Application for Pre-Submission Meeting Request

GL-MDC01 Guidance on reporting of adverse events in clinical investigations and performance studies

Cap 458 Act no VII of 2020, An Act to amend the Medicines Act
https://legislation.mt/eli/act/2020/7/eng

S.L. 458.59 Medical Devices and In-Vitro Diagnostic Medical Devices Provision On The Maltese Market Regulations https://legislation.mt/eli/sl/458.59/eng

EU legislations- Medical Devices and In-Vitro Diagnostic Medical Devices
https://health.ec.europa.eu/medical-devices-sector/new-regulations_en

MDCG 2021-08 Clinical investigation application/notification documents Guidance - MDCG endorsed documents and other guidance (europa.eu)

MDCG 2024-03 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices Guidance - MDCG endorsed documents and other guidance (europa.eu)

MDCG 2024-05 Guidance on content of the Investigator's Brochure for clinical investigations of medical devices Guidance - MDCG endorsed documents and other guidance (europa.eu)

MDCG 2021-06 Regulation (EU) 2017/745 Questions & Answers regarding clinical investigation Guidance - MDCG endorsed documents and other guidance (europa.eu)

2023/C 163/06 Commission Guidance on the content and structure of the summary of the clinical investigation report
https://eur-lex.europa.eu/legalcontent/EN/TXT/?uri=CELEX:52023XC0508(01)

ISO Standard 14155:2020 – Clinical investigation of medical devices for human subjects

List of Appendices

N/A

Signatures on file