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Medical Device White Paper Series

Medical device clinical investigations — What's new under the MDR?

An update

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1. Introduction

This paper was first published by BSI in 2018 and has been revised in light of the publication of BS EN ISO 14155:2020. The paper discusses important requirements for pre-market and post-market clinical investigations under the European Medical Device Regulation (2017/745) (MDR), relevant European guidance documents and BS EN ISO 14155:2020, and how this updated standard can help in meeting MDR requirements. The paper also addresses the importance of defining the regulatory purpose of a study, the relationship of a clinical investigation with quality management system (QMS) practices and strategies for conducting a successful clinical investigation, including the importance of defining the steps for its planning and conduct. Some of these steps can be carried out in parallel, while others will need to be sequentially followed. Knowing which ones can overlap will benefit the project and its timelines.

The conduct of a clinical investigation, also referred to as a clinical study in this paper, is one of the most time consuming, and resource intensive activities that a medical device manufacturer can face. For these reasons, manufacturers should ensure that the purpose of the clinical investigation is clear; all applicable regulations, common specifications (e.g. concerning device-specific requirements relevant for clinical investigations), international standards, European guidance documents and any national requirements and guidance documents, have been identified; all persons involved with the study understand their roles and responsibilities; and, the study is well organized and conducted in accordance with relevant QMS practices.

The clinical investigations discussed in this paper are generally conducted to meet regulatory requirements related to the generation of clinical data in support of safety and/or clinical performance for CE marking or maintaining the CE mark of the subject device. More than one clinical investigation may be needed. For this reason, manufacturers should clearly define the regulatory purpose for generating such data and identify the clinical development stage applicable to the clinical study to be conducted.

MDR Article 10(9) requires manufacturers of devices, other than investigational devices, to establish a QMS that ensures compliance with the MDR and that addresses among other aspects, product realization, including planning, design, development, production and service provision. Clinical investigations are, in most cases, part of the design process and, where post-market clinical follow-up (PMCF) investigations are conducted, intended to demonstrate ongoing device safety and clinical performance requirements. Thus, clinical investigations are activities that should be managed under the QMS in that they are generally intended to meet the requirements of the MDR.

The development of key standard operating procedures (SOPs) for managing the clinical investigation process, within the QMS, serves the same purpose as SOPs developed for other aspects of a manufacturer's processes. That is, they provide clarity, consistency, a means for avoiding errors and omissions, and they facilitate compliance with regulatory requirements.

SOPs for managing the clinical investigation process are applicable not only to manufacturers deciding to manage clinical investigations internally with company personnel, but also to those that need to outsource one or more clinical investigation activity to an external vendor. In the latter case, fewer internal SOPs may be needed if the SOPs of the external vendor are used.

The availability of persons who understand the medical device clinical investigation process, whether by training or experience or both, is critical for its successful implementation. In contrast, assigning persons with little or no experience or knowledge of clinical investigation requirements and management is associated with ineffective study management, which can lead to project delays, and, possibly, failure to achieve intended clinical data objectives.

2. MDR requirements for pre-market clinical investigations

2.1 General considerations

MDR Article 2(45) defines 'clinical investigation' as: any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.

A pre-market clinical investigation, namely, a clinical investigation with a device that has not yet been CE marked, will need to comply with the MDR. It should be noted, however, that clinical investigations initiated before 26 May 2021, the date of application of the MDR, were eligible to be conducted in compliance with the Medical Devices Directive (93/42/EEC) (MDD) or Active Implantable Medical Device Directive (90/385/EEC) (AIMDD) until completion of the study.

Clinical investigations conducted under the MDR will need to comply with any applicable common specifications, which are defined in MDR Article 2(71) as: a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.

A clinical investigation will also need to comply with any applicable requirements of the national competent authority(ies) and ethics committee(s). Relevant European harmonized standards, international standards and European and national guidance documents should also be taken into consideration. In addition, it is important that sponsors are fully versed in the state of the art in medical practice related to the device technology involved, including related practice guidelines or other device-specific guidance. This is important because the demonstration of compliance of a device with MDR safety and clinical performance requirements, for example, those specified in general safety and performance requirement (GSPR 1), must take account of the generally acknowledged state of the art.

The MDR sets out very detailed requirements regarding clinical investigations when compared with the MDD and AIMDD. That is, MDR Articles 62 through 82 address in a comprehensive manner:

- general requirements regarding clinical investigations conducted to demonstrate conformity of devices
- informed consent
- clinical investigations on subjects requiring special consideration, such as, incapacitated subjects, minors and pregnant or breastfeeding women
- ability of national authorities to maintain additional measures regarding certain categories of persons, such as those performing mandatory military service, persons deprived of liberty and others
- clinical investigation in emergency situations
- damage compensation
- application for clinical investigations
- assessment by Member States of the clinical investigation application
- conduct of the clinical investigation
- electronic system on clinical investigations
- clinical investigations of devices bearing the CE marking
- substantial modifications to clinical investigations
- corrective measures to be taken by Member States and Member State information exchange
- information from the sponsor at the end, temporary halt or early termination of a clinical investigation
- coordinated assessment procedure for clinical investigations

- review of coordinated assessment procedure
- recording and reporting of adverse events
- authority to establish additional details by means of implementing acts and
- requirements for clinical investigations not performed for establishing or verifying clinical performance, clinical benefit or safety

MDR Annex XV, Clinical Investigations, consists of three chapters: Chapter I, General Requirements; Chapter II, Documentation Regarding the Application for Clinical Investigation and Chapter III, Other Obligations of the Sponsor.

In spite of the detailed requirements included in the MDR, manufacturers with experience in conducting clinical investigations may find that many of these requirements are familiar. This is because similar requirements and procedures are described in the European harmonized standard, BS EN ISO 14155:2011, Clinical investigation of medical devices for human subjects — Good clinical practice, which has been revised and will be discussed later. Also, three European guidance documents were available to assist with compliance with clinical investigation requirements as specified in the Directives, and included:

- MEDDEV 2.7/4 on the need for, and general principles of, clinical investigations
- MEDDEV 2.7/2 Rev 2 on clinical investigation validation and assessment by competent authorities and
- MEDDEV 2.7/3 Rev 3 on serious adverse event (SAE) reporting

In fact, important aspects of the requirements in the MDR regarding clinical investigations were based on BS EN ISO 14155:2011 (see MDR 'Whereas' statement #64) and the European guidance documents listed above.

It is important to note that BS EN ISO 14155:2011 has been revised and replaced by BS EN ISO 14155:2020. During its revision every effort was made to avoid conflicts with the MDR and to take into consideration the expanded clinical investigation requirements in the MDR, while at the same time meeting international needs. The standard is expected to become a European harmonized standard; however, at the time of writing of this paper, its harmonization has not yet occurred and cannot be predicted due to delays in the overall harmonization process.

Regardless of its harmonization status, manufacturers are advised to purchase the standard and implement all applicable procedures and practices, as it reflects the state of the art regarding good clinical practice (GCP) for medical device clinical investigations.

Manufacturers should also be aware of a European guidance document, MDCG 2021-6, Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation (April 2021), developed by the Clinical Investigation and Evaluation (CIE) subgroup of the Medical Device Coordination Group (MDCG). The CIE assists the MDCG on issues relating to CIE of medical devices in accordance with the MDR. The guidance document is intended for sponsors of clinical investigations of medical devices conducted within the scope of the MDR.

2.2 New requirements under the MDR

The MDR introduces new requirements, in comparison with the Directives, which need to be carefully reviewed and addressed in applicable procedures for the conduct of clinical investigations under the MDR. The MDR requirements presented here are those that will most likely require changes in the conduct of a clinical investigation even if BS EN ISO 14155:2020 and European clinical investigation-related guidance documents have been followed.

2.2.1 Introduction of 'sponsor'

The MDR has introduced the term 'sponsor', defining it in MDR Article 2(49), as: 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.

This is important, because under the Directives, only the manufacturer or authorized representative was identified as the responsible party for the conduct of a clinical investigation. This resulted in some uncertainty regarding the regulatory responsibility of an independent clinical investigator who initiates a medical device clinical investigation.

Thus, under the MDR, the definition of 'sponsor' means that clinical investigators initiating clinical studies will be responsible for meeting MDR clinical study-related requirements; however, this does not prevent agreements on study conducted between investigators and manufacturers. It will be useful, however, for manufacturers intending to support the study or use the study results for regulatory purposes, to ensure that the investigator acting as a study sponsor is aware of sponsor-related requirements under the MDR.

2.2.2 Legal representative

Under MDR Article 62(2) requires that a legal representative be designated when the sponsor of a clinical investigation to be conducted in the European Union (EU) is not in the EU. The legal representative will be responsible for ensuring compliance with the sponsor's obligations and will be the addressee for all communications with the sponsor provided for in the regulation. The MDR allows, however, a Member State the option of not applying this requirement if the study is conducted solely on their territory, or on the territory of a third country, provided that the sponsor establishes at least a contact person on their territory. Unless exempted, this is an important new requirement that a non-EU sponsor conducting a clinical investigation in the EU will need to address.

2.2.3 Ethics committees

The responsibility of ethics committees is to evaluate a clinical investigation and determine whether ethical principles are being met. Requirements related to ethics committee composition and function were not specified in the AIMDD or MDD, nor are they specified in the MDR; however, MDR Article 62(3) requires that ethical review of a clinical investigation is performed by an ethics committee in accordance with national law. The MDR also requires that Member States ensure that the procedures for review by ethics committees are compatible with the procedures set out in the MDR and that at least one lay person participates in the ethical review.

Thus, the ethics committee approval process is not harmonized, which has led to and will continue to lead to variability in ethics committee procedures and required documents and timeframes, within the same Member State, and among different Member States.

Ethics committee approval timelines range from 30 to 90 days or more in some cases.

To avoid delays in ethics committee approval, sponsors should not simply leave this process to the investigator without ensuring that all submission requirements will be met. This means that sponsors or, if outsourced, the selected contract research organization (CRO), should:

- understand the regulatory category of the study (i.e. pre-market, post-market) and type of study (registry, observational, interventional, other)
- be informed about the procedural and documentation requirements of each ethics committee
- understand the need for a signed site contract
- determine whether translations are needed and
- determine who needs to sign which document

2.2.4 Risk management

The MDR includes very specific requirements regarding risk management and its relationship to how clinical investigations are planned, documented and conducted. That is, MDR Article 62(4)(e) specifies that clinical investigations can be conducted only if anticipated benefits to subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition must be constantly monitored. This means of course that the MDR requires that the foreseeable risks be identified before the clinical investigation is conducted. In addition, MDR Article 62(4)(i) requires that these risks be as little as possible and furthermore, that the risk threshold be specifically defined in the clinical investigation plan (CIP) and constantly monitored.

BS EN ISO 14155:2020 includes significant reinforcement of risk management throughout the clinical investigation process, from planning to the consideration of study results, when compared with the previous edition, including the new Annex H (informative), application of BS EN ISO 14971:2019 to clinical investigations. For example, Subclause 6.2.1 of BS EN ISO 14155:2020 requires the predefinition of risk acceptability thresholds and the conduct of risk assessment whenever these thresholds are reached or exceeded to determine whether actions will need to be taken. In addition to representing the state of the art, it facilitates compliance with MDR Article 62(4)(i). Other important aspects of risk management are addressed throughout the standard.

It should be mentioned that in addition to BS EN ISO 14155:2020 being the relevant standard for facilitating compliance with MDR requirements for medical device clinical investigations, BS EN ISO 14971:2019 is the relevant standard regarding risk management. At the time of writing of this paper, however, neither standard has been harmonized to allow a presumption of conformity with the MDR. For this reason, it is imperative that the provisions of the standards that are applied be evaluated to ensure that there is no conflict with the requirements of the MDR. If this is done, conformity with both standards will facilitate compliance with the MDR in very important ways.

2.2.5 Competent authority approval

The responsibility of competent authorities is to evaluate a clinical investigation application and determine whether regulatory requirements are being met. MDR Article 70, Application for clinical investigations, specifies the steps in the application process.

Article 70(1) requires that the application be submitted by means of the electronic system referred to in Article 73, namely, EUDAMED. As discussed later, however, the full functionality of EUDAMED has been delayed. In its absence, a European guidance document, MDCG 2021-08, Clinical investigation application/notification (May 2021), which provides links to a series of clinical investigation application and notification templates to support the application process. It is planned that these templates will be withdrawn once the EUDAMED

module for clinical investigations is fully functional. It should be noted, however, that the guidance stresses the importance of checking with the individual Member State in which the clinical investigation is planned to be conducted to identify any specific national requirements.

The clinical investigation application requirements also specify various time periods that must be respected. For example, Article 70(2) requires that within 1 week of making any change, the sponsor updates any change in the submitted documentation. A range of other timeframes are also specified.

According to Article 70(5), the date that the Member State notifies the sponsor that the application is complete is considered the validation date of the application. Article 70(6) provides that during the period when the application is being assessed, the Member State may request additional information from the sponsor.

Article 70(7) specifies that clinical investigations with class I or non-invasive class IIa and class IIb devices may be initiated immediately after the validation date unless otherwise stated by national law, provided that a negative opinion valid for the entire Member State has not been issued by the applicable ethics committee.

For devices other than class I or non-invasive class IIa and class IIb devices, the clinical investigation may be initiated as soon as the Member State has notified the sponsor that the investigation has been authorized. This must be within 45 days of the validation date, although the Member State may extend this by 20 days for the purpose of consulting with experts.

As stated previously, MDR Annex XV, Chapter II, lists the documentation that must be included in the clinical investigation application. It is also possible that national competent authorities may request additional documentation, which is important to address during clinical investigation planning to avoid delays during the application process.

2.2.6 Inspection of investigation sites

MDR Article 72(5) introduces the requirement that Member States inspect, at an appropriate level, investigation site(s) to check that clinical investigations are conducted in accordance with the requirements of the MDR and the CIP. This means that sponsors should ensure that the relevant investigation site involved in the conduct of a clinical investigation with the sponsor's medical device is adequately prepared for such an inspection. The areas inspected will depend upon the practices and procedures of the Member States.

2.2.7 Procedures for immediate identification or recall

MDR Article 72(6) introduces a new requirement, which is that the sponsor establishes a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the clinical investigation. It is expected that this procedure will be managed within the manufacturer's QMS.

2.2.8 Coordinated assessment procedure for clinical investigations

MDR Article 78, Coordinated assessment procedure for clinical investigations, introduces a new process for submitting a clinical investigation application where the investigation is planned to be conducted in more than one Member State. The sponsor may submit a single application, transmitted by means of the electronic system referred to in MDR Article 73, to all Member States in which the investigation is to be conducted. The sponsor must propose that one of the Member States acts as the coordinating Member State. Initially, this procedure will involve only Member States voluntarily agreeing to apply the procedure. It becomes mandatory, however, on 27 May 2027, unless this date changes as a result of a review that is to be conducted by the European Commission by 26 May 2026.

2.2.9 SAE reporting to Member States

Under MDR Article 80, Recording and reporting of adverse events that occur during clinical investigations, paragraph 2 states:

The sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following by means of the electronic system referred to in Article 73:

(a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

(b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

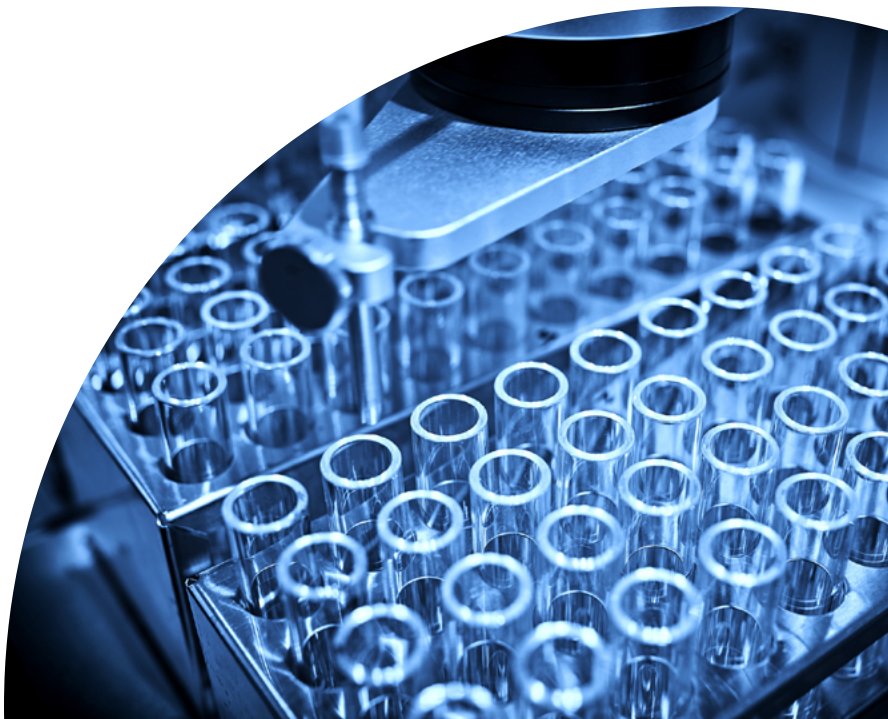
(c) any new findings in relation to any event referred to in points (a) and (b).

The need to report only SAEs that have a causal relationship with the investigational device, comparator or investigation procedure is an important difference from the AIMDD and MDD, which required that all SAEs be immediately notified to all competent authorities of the Member States in which the clinical investigation was being performed.

It should also be noted that MDR Article 120(11) states:

Clinical investigations which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC prior to 26 May 2021 may continue to be conducted. As of 26 May 2021, however, the reporting of serious adverse events and device deficiencies shall be carried out in accordance with this Regulation.

Two MDCG guidance documents on safety reporting under the MDR have been developed: Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (MDCG 2020-10/1) and Clinical investigation summary safety report form v1.0 (MDCG 2020-10/2). These documents address various issues including safety reporting of clinical studies that have begun under the Directives, how safety reports should be submitted to National Competent Authorities in the absence of EUDAMED (the delay in EUDAMED implementation is discussed later) and other issues.



2.2.10 Monitoring

MDR Article 72(2), Conduct of a clinical investigation, states the following:

In order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical investigation is in compliance with the requirements of this Regulation, the sponsor shall ensure adequate monitoring of the conduct of a clinical investigation. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical investigation including the following:

(a) the objective and methodology of the clinical investigation; and

(b) the degree of deviation of the intervention from normal clinical practice.

This means that under the MDR, appropriate monitoring is a requirement and not an option.

2.2.11 Independence of monitors

Monitors are appointed by sponsors to check on the progress of a clinical investigation to ensure that it is being conducted in compliance with the CIP, established GCPs and other applicable regulatory requirements.

There is an important new restriction regarding the appointment of monitors, which is specified in MDR Annex XV, Clinical Investigations, Chapter III, Section 4, which states: The Sponsor shall appoint a monitor that is independent from the investigational site to ensure that the investigation is conducted in accordance with the CIP, the principles of good clinical practice and this Regulation.

The MDR Article 2(47) defines the CIP as: a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation.

This is an important new requirement because some medical device clinical investigations have been monitored by persons who are employed by an investigational site or where a clinical investigator maintains a unit for monitoring a clinical study in which the investigator is involved. This new requirement means that these practices are not possible for clinical investigations conducted under the MDR. That is, sponsors will need to ensure that the monitor is not part of a unit within the clinical investigation site where the clinical investigation is being conducted.

2.2.12 Prohibition of waivers

Annex XV, Clinical Investigations, Chapter II, Section 3, specifies detailed requirements regarding the CIP. Section 3.10 indicates that the CIP must contain a: Policy regarding follow-up and management of any deviations from the CIP at the investigational site and clear prohibition of use of waivers from the CIP.

The clear prohibition of use of waivers is the new requirement. Although the consideration of exercising of a waiver regarding some aspect of the CIP may not be a frequent occurrence, the sponsor of the clinical investigation needs to be aware of the prohibition of a waiver. That is, the sponsor should be particularly careful in developing a CIP that meets regulatory and data quality objectives but is not so stringent as to create unnecessary difficulties in compliance.

2.2.13 GCP inspections by sponsors

MDR Annex XV, Chapter III, Section 6 requires that sponsors provide evidence that the clinical investigation is being conducted in line with GCPs, for instance through internal or external inspection. This requirement was not included in the Directives. Revised ISO 14155 includes Annex J (informative), Clinical investigation audits, which is a new annex that provides general guidance on the areas that can be covered in these inspections.

2.2.14 Relationship between clinical investigation and clinical evaluation

MDR Annex XIV, Part A, Section 1(a), last indent, requires that the clinical evaluation plan includes information on the clinical development plan, specifically:

a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria.

Section 2.4, Chapter I of Annex XV, Clinical investigation, requires clinical investigations to be in line with the clinical evaluation plan.

Section 1.5, Chapter II of Annex XV, requires that the clinical investigation application to include, among other information, details and/or reference to clinical evaluation plan.

This means that clinical investigations need to be consistent with the information contained in the clinical development plan, which is part of the clinical evaluation plan.

Section 3.6.1, Chapter II of Annex XV, requires the CIP to include, among other detailed information, type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan. Again, this means that the information contained in the CIP and the clinical evaluation plan need to be consistent.

3. MDR requirements for PMCF investigations

3.1 General considerations

MDR Article 74, Clinical investigations regarding devices bearing the CE marking, refers to a PMCF investigation as a clinical investigation conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking.

Manufacturers should be careful to distinguish a PMCF investigation from other types of PMCF, some of which are referred to in MDR Annex XIV, Part B, Section 6.2, such as: gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data or evaluation of suitable registers. These types of PMCF or PMCF activities are different from a PMCF investigation, which is subject to a series of requirements, specified in MDR Article 74, some of which are the same as those applicable to pre-market clinical investigations.

3.2 PMCF investigations involving additional and burdensome procedures

MDR Article 74(1) requires that where a PMCF investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome, the sponsor must notify the Member States concerned at least 30 days prior to its commencement by means of the electronic system referred to in Article 73, and include the documentation referred to in Chapter II of Annex XV as part of the notification. This documentation is the same type of documentation required for pre-market clinical investigations. MDR Article 74(1) also states that points (b) to (k) and (m) of Article 62(4); Articles 75, 76 and 77 and Article 80(5) and (6), and the relevant provisions of Annex XV apply to PMCF investigations.

This means that the sponsor of a PMCF investigation that is conducted in accordance with the device IFU and/or operating manual needs to comply with the specified provisions indicated in the last sentence of Article 74(1) but does not need to notify the competent authority of the PMCF investigation.

For these reasons, it is very important to determine whether the PMCF investigation is planned to be conducted under normal conditions of use or whether any additional procedures (e.g. additional blood analyses, diagnostic X-rays or scans or other procedures) are planned.

A new annex of BS EN ISO 14155:2020 should prove useful in considering factors that are important for complying with MDR Article 74. That is, Annex I (informative), Clinical development stages, includes Section I.6, Burden to subjects, which provides information on the categorization of clinical investigations based on interference with normal clinical practice, distinguishing between interventional and non-interventional studies.

3.3 PMCF investigations and adverse event reporting

Regarding compliance with adverse event reporting, MDR Article 80(5) requires that in the case of PMCF investigations, the provisions on vigilance laid down in MDR Articles 87 to 90 and in the acts adopted pursuant to MDR Article 91 apply.

MDR Article 80(6), however, states the following: Notwithstanding paragraph 5, this Article shall apply where a causal relationship between the serious adverse event and the preceding investigational procedure has been established.

By 'this Article shall apply', Article 80(6) is referring to MDR Article 80(1) through (4).

That is, manufacturers will need to determine whether a serious incident has occurred, which needs to be reported under MDR vigilance requirements as specified in MDR Articles 87 to 90 or whether a SAE has occurred, which meets the requirements of Article 80(6) and needs to be recorded and reported as specified in Article 80(1) to (4).

4. MDR requirements regarding other clinical investigations

MDR Article 82(1), Requirements regarding other clinical investigations, specifies that clinical investigations, not performed for any of the purposes listed in MDR Article 62(1), must comply with the provisions listed below:

- MDR Article 62, General requirements regarding clinical investigations conducted to demonstrate conformity of devices, specifically:
  - paragraph (2), which concerns the need for a sponsor not established in the EU to appoint a natural or legal person in the EU as its legal representative and
  - paragraph (3), which requires that the rights, safety, dignity and well-being of subjects be protected and that clinical investigations must be subject to scientific and ethical review
- MDR Article 62(4), which lists the conditions that must be met to conduct a clinical investigation, specifically:
  - point (b), which requires that a negative opinion from an ethics committee, valid for the entire Member State, has not been issued
  - point (c), which specifies need for a sponsor, legal representative or where relevant, contact person, to be in the EU
  - point (d), which requires protection of vulnerable populations in accordance with Articles 64 to 68
  - point (f), which specifies requirements for informed consent when the subject is unable to provide it
  - point (h), which requires a safeguard of the rights subjects concerning their physical and mental integrity and of privacy and protection of data
  - point (l), which requires that the investigational device conforms to applicable GSPRs
- MDR Article 62(6), which requires that the investigator has a profession recognized in the Member State concerned and that any other personnel involved in conducting the clinical investigation are appropriately qualified.

MDCG 2021-6, the European guidance that consists of questions and answers related to clinical investigations, mentioned previously, states that if the clinical investigation is not performed for conformity purposes, Article 82 of the MDR applies.

Furthermore, MDR Article 82(2) requires that to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations not performed for any of the purposes listed in Article 62(1), each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned.

This means that manufacturers should check on and comply with any national requirements that apply to the conduct of such types of clinical investigations.

5. Alternative interpretation of MDR Articles 74 and 82

MDCG 2021-6 concludes that Article 74(1) applies only to PMCF investigations that involve additional invasive or burdensome procedures. This conclusion is expressed in response to Question 7 of the guidance, which is 'A CE marked medical device is planned to be further investigated in a clinical investigation – how does a sponsor determine the regulatory pathway for this clinical investigation'? That is, the answer to the question states in part: ...If safety and performance of a CE marked device is being further investigated and Article 74(1) of the MDR is not applicable, Article 82 of the MDR may apply.

If the safety and performance of a CE marked device is being further investigated, however, Article 74(1) will apply. This is clearly indicated in the third and last sentence of Article 74(1), which states: Points (b) to (k) and (m) of Article 62(4), Articles 75, 76 and 77, and Article 80(5) and (6), and the relevant provisions of Annex XV shall apply to PMCF investigations.

That is, as written, this requirement applies to any PMCF investigation whether it involves additional invasive or burdensome procedures or not. This is because this part of the regulation does not in any way refer to PMCF investigations involving additional invasive or burdensome procedures.

In addition, MDCG 2021-6 includes a flow chart in Annex I, Clinical investigation under MDR — regulatory pathway, which indicates that MDR Article 74(1) applies only to a PMCF investigation involving additional burdensome and/or invasive procedures and that MDR Article 82 applies to PMCF investigations that do not include these types of procedures.

It should be noted that this interpretation allows Member States to define any additional requirements for such investigations. These additional requirements can include the need to notify the Member State of the PMCF investigation, which conflicts with the MDR if MDR Article 74(1) is understood to apply to any PMCF investigation, including an investigation that does not involve additional invasive or burdensome procedures. It is very likely that the text of Article 74(1) and the manner in which it has been interpreted in MDCG 2021-6 will be reexamined.

In the meantime, sponsors are strongly advised to comply with national requirements for conducting PMCF investigations regardless of the Member State interpretation of MDR Article 74(1) and Article 82.

6. EUDAMED

The EUDAMED database will be extremely important in the implementation of the MDR and is intended to have many functions, including the registration of devices and economic operators, and the receipt of vigilance and field safety reports. It will also serve an important function regarding the fulfilment of MDR clinical investigation requirements.

Unfortunately, EUDAMED was not fully functional on the date of application of the MDR, which was 26 May 2021, having been extended from 26 May 2020. The launch date is now planned for May 2022 to coincide with the date of application of the In Vitro Diagnostic Medical Devices Regulation (2017/746) (IVDR).

For this reason and until EUDAMED becomes fully functional, MDR Article 123, Entry into force and date of application, Section 3(d), provides a derogation of the need to enter information into the EUDAMED database, including information concerning clinical investigations. It is important that manufacturers carefully review this section of the MDR to understand which requirements are affected, so that they can be addressed in relevant procedures, which will require modification once EUDAMED becomes fully functional.

As listed in Section 3(d), derogation of requirements related to clinical investigations and reporting of SAEs and serious incidents apply to the following:

- Articles 70 to 77
- Article 78(1) to (13)
- Articles 79 to 82
- Articles 87 and 88
- Article 89(5) and (7)
- Article 89(8), third subparagraph and
- Article 90

In accordance with Section 3(d), the obligations and requirements related to EUDAMED will apply 6 months after the date of publication of a notice in the Official Journal of the European Union, described in MDR Article 34, Functionality of EUDAMED, indicating that EUDAMED is fully functional. Until EUDAMED is fully functional, the corresponding provisions of the AIMDD and MDD will apply.

As indicated previously, MDCG 2021-08 provides links to a series of clinical investigation application and notification templates to support the application process until EUDAMED becomes fully functional.

7. Regulatory purpose of clinical investigations

7.1 Regulatory purpose of a pre-market clinical investigation

Pre-market clinical investigations are generally conducted to generate clinical data in support of safety and/or clinical performance for CE marking. They may also be conducted in stages as more than one investigation may be needed to generate the necessary clinical data. In this regard, MDR Annex XIV, Part A, Section 1(a), last indent, requires that the following be included in the clinical evaluation plan: a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations….

BS EN ISO 14155:2020, Annex I (informative), Clinical development stages, referred to previously, describes the types of clinical investigations typically associated with different clinical stages. The clinical stages described include the pilot, pivotal and post-market stages; the types of clinical investigation designs described include exploratory, confirmatory and observational and the descriptors of clinical investigations include first in human, early feasibility, traditional feasibility, pivotal, post-market and registry.

In addition, the conduct of a clinical investigation for CE marking purposes is directly related to the requirements in MDR Article 61, Clinical evaluation. This is because Article 61 requires that confirmation of conformity with relevant GSPRs in MDR Annex I, the evaluation of undesirable side-effects and the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, must be based on clinical data providing sufficient clinical evidence. Sections 1 and 8 are also referred to as GSPRs 1 and 8.

GSPR 1 requires that devices achieve the performance intended by the manufacturer, are safe and effective, that any risks associated with device use are acceptable when weighed against the benefits to patients, and that the devices are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art. GSPR 8 requires that all known and foreseeable risks, and any undesirable side-effects, be minimized and acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.

Clinical data from a clinical investigation may be needed to clarify risks associated with the use of the device or to validate risk control measures, such as those related to the design, usability or information contained in the IFU.

In addition to GSPRs 1 and 8, the manufacturer will need to determine whether other GSPRs, for example, GSPR 5 related to use error, or other GSPRs, will require confirmation of conformity based on clinical data. Thus, the regulatory purpose of the clinical investigation for CE marking purposes is the generation of clinical data to satisfy identified GSPRs.

These determinations will have a direct effect on clinical investigation objectives and will need to be addressed carefully.

MDR Article 61(2) also provides an option that did not exist under the Directives, which applies to all class III devices and class IIb active devices intended to administer and/or remove a medicinal product, as referred to in MDR Annex VIII, Section 6.4 (Rule 12). This option allows a manufacturer to consult an expert panel, referred to in Article 106, Provision of scientific, technical and clinical opinions and advice, before the clinical evaluation and/or investigation. The purpose is for the expert panel to review the manufacturer's intended clinical development strategy and proposals for clinical investigation. The manufacturer must give due consideration to the views expressed by the expert panel and the consideration must be documented in the clinical evaluation report. Information on expert panels established under the MDR can be found on the European Commission website.

7.2 Regulatory purpose of a PMCF investigation

The regulatory purpose for conducting a PMCF investigation can be one or more of the aims listed in MDR Annex XIV, Part B, Section 6.1. These aims include:

- confirming the safety and performance of the device throughout its expected lifetime
- identifying previously unknown side-effects and monitoring the identified side-effects and contraindications
- identifying and analysing emergent risks on the basis of factual evidence
- ensuring the continued acceptability of the benefit-risk ratio referred to in Sections 1 and 9 of Annex I and
- identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct

One or more of these aims should be identified and documented in the PMCF plan.

MDR Annex XIV, Part B, Section 6.2, specifies the required elements of a PMCF plan. A guidance document, MDCG 2020-7, Post-market clinical follow-up (PMCF) plan template — A guide for manufacturers and notified bodies (April 2020), has been developed to assist manufacturers in complying with MDR requirements concerning the compilation of the plan. Manufacturers are advised to use this guidance.

MDR Annex XIV, Part B, Section 7 requires the manufacturer to analyse the findings of the PMCF and document the results in a PMCF evaluation report, which must be considered part of the clinical evaluation report and technical documentation. A guidance document, MDCG 2020-8, Post-market clinical follow-up (PMCF) evaluation report template — A guide for manufacturers and notified bodies (April 2020), has also been developed to assist manufacturers in complying with MDR requirements concerning the compilation of the report.

MDR Annex XIV, Part B, Section 8 requires the conclusions of the PMCF evaluation report to be taken into account in clinical evaluation and risk management. If the PMCF indicates the need for preventive and/or corrective measures, the manufacturer must implement them.

In addition, it is important to note that, from an MDR point of view, planning the conduct of any type of PMCF is within the post-market surveillance (PMS) system. This is because, MDR Annex III, Technical documentation on post-market surveillance, Section 1.1, requires that the PMS plan includes a PMCF plan or a justification of why a PMCF is not applicable.

8. QMS and clinical investigations

8.1 QMS and pre-market clinical investigations

It can be anticipated that most manufacturers will demonstrate compliance with the MDR by means of conformity assessment based on a QMS and assessment of technical documentation, as specified in MDR Annex IX. Section 2.2(c) requires that the documentation to be submitted for the assessment of the QMS includes an adequate description of: the procedures and techniques for monitoring, verifying, validating and controlling the design of the devices and the corresponding documentation as well as the data and records arising from those procedures and techniques. Eight different elements that the procedures and techniques need to address are specified and, in brief, are:

- strategy for regulatory compliance
- identification of applicable GSPRs
- risk management
- clinical evaluation
- solutions for fulfilling the applicable specific requirements regarding design and construction
- solutions for fulfilling the applicable specific requirements regarding the information to be supplied with the device
- device identification procedures and
- management of design or QMS changes

A pre-market clinical investigation is part of the design and development process because it is a design validation activity if it is intended to demonstrate that the device complies with regulatory requirements. Thus, the clinical investigation and its documentation should be managed within the company's QMS and be addressed during design and development planning, design and development reviews and design validation.

The SOPs that can be helpful in conducting a clinical investigation are discussed later in this paper in the section, 'Clinical investigation SOPs'.

8.2 QMS and PMCF investigations

The results of PMCF investigations will need to be documented in the PMCF evaluation report. They will also need to be considered in updating the CER, risk management, PMS report, periodic safety update report, and for implantable devices and class III devices, the summary of safety and clinical performance. The results of the PMCF investigation may also be linked to the need for corrective action or preventive action, or in some cases, to validate a design change made in the post-market period.

For these reasons, manufacturers are encouraged to develop QMS procedures that will address these requirements and linkages to help ensure compliance with these interconnected regulatory requirements.

9. Strategies for conducting successful clinical investigations

9.1 Knowledgeable clinical affairs personnel

The importance of assigning responsibilities for managing clinical investigations, including PMCF investigations, to knowledgeable persons cannot be overemphasized. This is because clinical investigations are complex and the data generated are expected to be ethically and scientifically valid, reliable and robust. If not conducted properly, mistakes made could jeopardize the success of the project for which they are being conducted, such as, market entry or continued presence on the market.

For these reasons, clinical study personnel need to be aware not only of the regulatory requirements applicable to clinical study conduct, but also of the unique aspects of medical device clinical studies. For example, in contrast with many types of pharmaceutical studies, the success of many types of medical device clinical studies is heavily dependent on the quality and clarity of the CIP in describing how the medical device needs to be studied, the instructions for use, operating manual (where applicable), possible training needed, the expertise of the medical practitioner in the use of a particular medical device technology or ability of a lay person to use the device.

Thus, it is strongly advised that clinical study management personnel have either the relevant experience or receive appropriate training in the conduct of medical device clinical studies before assuming responsibility for this important activity.

Where sponsors of medical device clinical studies lack adequate internal resources, outsourcing of various responsibilities may be advisable to ensure that unacceptable risks are avoided by involving personnel with insufficient experience.

9.2 Clinical investigation SOPs

Sponsors of clinical investigations will need to develop clinical investigation-related SOPs to ensure compliance with the MDR, BS EN ISO 14155:2020, any other applicable standards and requirements of other regulatory jurisdictions where a clinical investigation is to be conducted. Any conflicting requirements should be identified and resolved. The SOPs should also take into consideration any official European guidance documents developed to aid compliance with the MDR.

The specific SOPs that a sponsor develops will depend upon the responsibilities of the sponsor in the development and management of the clinical investigation and whether any activities are outsourced. If all activities are managed in-house, clinical investigation SOPs should be sufficiently comprehensive to ensure compliance to applicable requirements, consistency and efficiency, and the avoidance of costly mistakes and omissions throughout the entire clinical investigation process. For example, sponsors may wish to consider developing SOPs that address the following aspects of clinical investigation conduct:

- regulatory requirements applicable to location of clinical study sites (regional and local)
- development and amendment of CIP
- development of the investigator's brochure
- development of an informed consent form according to regional and national requirements
- clinical vendor qualification, selection and management (e.g. CRO, central laboratory, other)
- compliance with regional and national requirements for ethics committee approval
- regulatory authority submission process
- conduct of the clinical investigation (responsibilities, procedures, staff qualifications, project-related training, CRO oversight where applicable, other)

- clinical site qualification, selection and management
- monitoring procedures
- adverse event reporting
- biostatistics, data collection and management
- document controls related to clinical studies, including management of records and study filing system
- data privacy requirements
- device accountability

It is important that these procedures are developed and controlled within the sponsor's QMS, where one exists, or in compliance with QMS principles and document controls.

Where certain activities of the clinical investigation are outsourced, the sponsor should ensure that the selected vendor is sufficiently qualified to provide the needed service. For example, vendors should be experienced in medical devices, operate under a QMS, have the necessary resources available to respond to client needs expeditiously and other characteristics based on the needs of the clinical investigation project.

9.3 Planning a medical device clinical investigation

9.3.1 Elements of the planning process

A well-organized planning process provides a means of understanding what needs to be done and when, whether activities need to be sequential or can overlap to save time and who is responsible for the various activities.

It is evident that the way that this process can be managed varies. Table 1 provides an example of an approach for planning a clinical investigation to address activities before the study start, during study conduct and close-out activities. Other approaches may be effective and should be based on the purpose and type of clinical investigation, the medical device being studied, organization responsible for study conduct and possibly other factors. The activities listed in Table 1 are not intended to be all inclusive. BS EN ISO 14155:2020 addresses clinical investigation planning in significant detail.

Table 1. Example of an approach for planning a clinical investigation

Set-up phase	Enrollment phase	Close out phase
Project team set-up	Training and site initiation	Site close out
Purpose and study design	Monitoring	Document archiving
Project management	Data collection and management	Statistics
Vendor selection	Adverse events and device deficiencies	Clinical study report
Development of CIP	Protocol deviations	Publications
Site selection	Device accountability	
Other regulatory/clinical documents	Audits	
Site agreements and EC / CA submissions		
Device release for clinical study		

9.3.2 Purpose of the clinical investigation

As discussed previously, medical device clinical investigations are generally performed for regulatory purposes, but this is not always the case. Thus, the purpose for conducting the clinical investigation should be agreed at the beginning of the planning process as it will have a direct effect on the regulations and requirements that are applicable, the design of the study and clinical data that will need to be generated.

Regardless of the purpose, the clinical investigation will need to be designed to generate scientifically valid data suitable for the particular purpose. Section 9.3.1 of the European guidelines on clinical evaluation (MEDDEV 2.7/1 Rev 4) provides helpful guidance on study design issues that can affect methodological quality and scientific validity, such as, the adequacy of the sample size and power calculation, endpoints, controls and other design considerations.

9.3.3 Project team

The persons participating in the project team should be identified, their roles and responsibilities defined and their competence established based on qualifications, education, training or experience. The specific roles will depend upon the sponsor's organization, the medical device, type of clinical investigation and whether any roles are outsourced. Typical roles, however, include: the project manager, medical affairs function, product specialist, regulatory affairs function, biostatistician, data manager and study monitor. Depending on the risks associated with the device, a data safety monitoring board or a clinical events committee can be appointed. Other entities, such as centralized laboratories or an independent review committee to ensure homogeneous patient selection, may also be involved.

9.3.4 Development of the CIP

The importance of CIP document in the conduct of a medical device clinical investigation cannot be overstated. MDR Annex XV, Section 3 and Annex A (normative) of BS EN ISO 14155:2020, specify the information that should be included in the CIP. If the clinical investigation is being conducted under the MDR, it is advisable to structure the CIP in accordance with the elements as listed in the MDR; however, the standard should be consulted when it provides additional detail for a required CIP element.

The CIP should include clearly defined objectives and endpoints, intended purpose, patient population, suitable inclusion and exclusion criteria and any necessary medical, regulatory and statistical input. The CIP should be a controlled document, managed within an organization's QMS, where one has been established or in compliance with QMS principles and document controls. At a minimum, both paper and electronic copies of revisions should be carefully checked to avoid mix-up. Regardless of the language in which the CIP is written, frequently in English, it should be written to facilitate understanding with correct grammar and spelling. While this may seem obvious, these practices are not always followed, which can lead to unnecessary misunderstandings and delays in the project.

9.3.5 Other study-related documents

The planning phase needs to ensure the availability of other important study-related documents, such as: the informed consent form used to record consent from study subjects to participate in the study; case report form (CRF) designed to record all information to be reported to the sponsor on each subject; IFU, which includes the intended purpose and any indications, contraindications, warnings and instructions for using the device; investigator's brochure (IB) and, other documents, such as, the statistical analysis plan, risk management documentation, insurance documentation and agreement between the sponsor and investigational site.

A strong correlation exists among many of these documents and the CIP, which means that inconsistencies among the documents should be avoided, such as, variations in intended use statements in the CIP and other documents, inconsistent descriptions of contraindications or warnings and revisions of documents referenced in the CIP that differ from the revision level of the official documents.

9.3.6 Site selection

The selection of the clinical study site(s) is a critical step in the planning of any clinical investigation and has a direct effect on study success. The selection of an inadequate site can lengthen the duration of a clinical study and, in the worst case, lead to project failure. For this reason, study sites should be carefully chosen.

The recommended steps in selecting a study site are, at a minimum, the following:

- visit of the site by an expert in the device to be studied and a clinical study expert
- check of the availability of potentially eligible subjects and suitability of facilities and equipment
- assessment of the knowledge of study site personnel regarding GCPs, specifically pertaining to medical devices
- check of site resources, organization and skills
- assessment of ethics committee/investigational review board timelines

Too frequently, manufacturers sponsoring a clinical investigation have identified a key opinion leader (KOL), but not adequately evaluated the KOL's clinical site to ensure that it can enroll study subjects at an acceptable rate and has the necessary resources to provide the required services in a timely and compliant fashion.

9.3.7 Monitoring

Monitoring is a quality-related tool to determine whether clinical investigation activities are performed as required and that deficiencies can be identified and corrected.

Recommendations for ensuring effective study monitoring include:

- following the procedures related to monitoring described in BS EN ISO 14155:2020
- developing a monitoring plan, which will describe monitoring activities for a specific clinical investigation
- ensuring that monitoring is performed by a qualified study monitor (clinical research associate) with relevant education, training and experience
- maintaining regular contact with study sites to ensure that study requirements are being met and any problems or deviations can be addressed in a timely fashion
- considering risk-based monitoring, where the monitoring plan for a clinical investigation is based on the reduction of risks that could affect the collection of critical data or performance of critical study activities
- exercising considerable care when monitoring remotely to ensure full compliance with regulatory requirements

9.3.8 Data collection and management

Clinical data generated during a clinical investigation are usually collected on a CRF, which is a set of printed, optical or electronic documents designed for recording all information on each subject of a clinical investigation and reported to the sponsor as required by the CIP. Data management concerns the management of the collected data.

The MDR does not specify requirements concerning CRFs or data management other than requiring that data management be included in the CIP. Instead, the details regarding CRFs and data management are provided in BS EN ISO 14155:2020.

9.3.9 Cost considerations

Performing a pre-market clinical investigation can be the most expensive activity involved with CE marking a new medical device or maintaining the CE mark. The cost of sponsoring a clinical investigation depends upon several factors, such as:

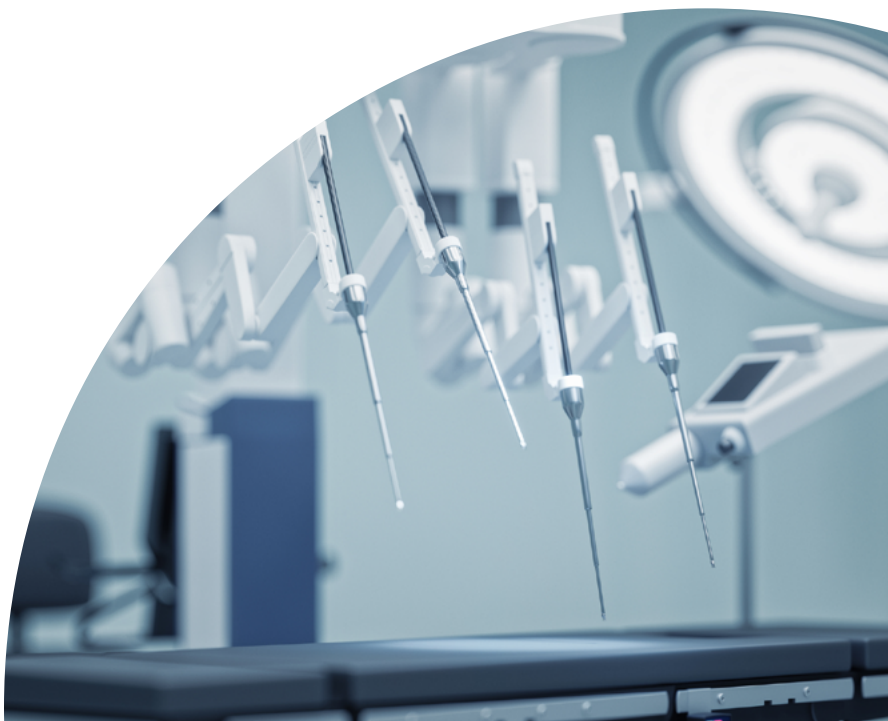
- complexity and duration of the study
- number of study subjects
- cost of the investigational device
- treatment and number of follow-up visits and type of checks made during the follow-up period
- number of countries involved
- number of study sites
- need for centralized laboratories
- whether study is managed in-house or by external vendors

Clearly, a determination of study costs is a critical element in the clinical investigation planning process. Thus, oversimplification of the process, which can lead to an underestimation of costs, should be avoided.

10. Conclusion

A successful clinical investigation is one that generates scientifically valid clinical data, reaches medically and scientifically sound study conclusions and is completed within planned time frames. This means that sponsors, investigators, clinical monitors and others involved with the clinical investigation, need to fully understand, and comply with applicable regulatory requirements, standards and guidance documents. In addition, they should:

- ensure that the clinical investigation process is in conformity with BS EN ISO 14155:2020
- ensure the involvement of qualified personnel in the planning and conduct of the clinical investigation
- ensure that appropriate QMS principles are followed throughout the clinical investigation process, including the development of relevant SOPs and control of clinical investigation-related documents
- ensure that an appropriate, compliant study design is developed
- carefully select clinical study sites based on factors that are important for the study, such as subject recruitment rate, resources and knowledge of GCPs, and not solely related to the presence of a KOL
- avoid underestimating the knowledge, qualified resources and activities needed to successfully complete a medical device clinical investigation



11. Further reading

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. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20200424

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MDCG 2021-08, Clinical investigation application/notification documents (May 2021). https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-8_en.pdf

MDCG 2020-10/1, Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 https://ec.europa.eu/docsroom/documents/41183?locale=en

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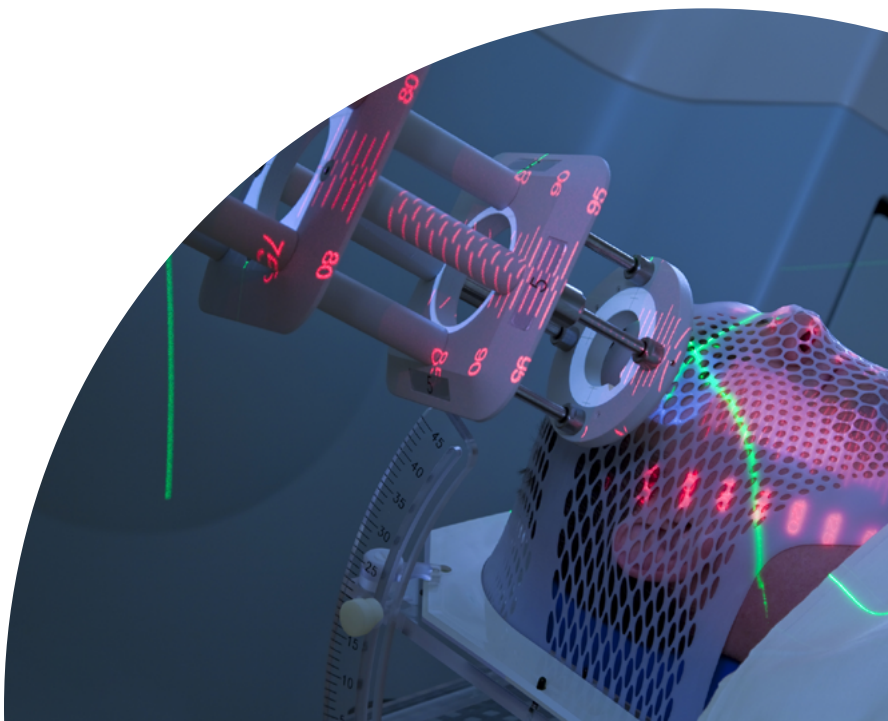

Author

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- *The proposed EU regulations for medical and in vitro diagnostic devices: An overview of the likely outcomes and consequences for the market,* Gert Bos and Erik Vollebregt
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- *Guidance on MDCG 2019-9: Summary of Safety and Clinical Performance,* Amie Smirthwaite, RMQ+
- *CER generation,* Amy Smirthwaite, RMQ+

Forthcoming white papers

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