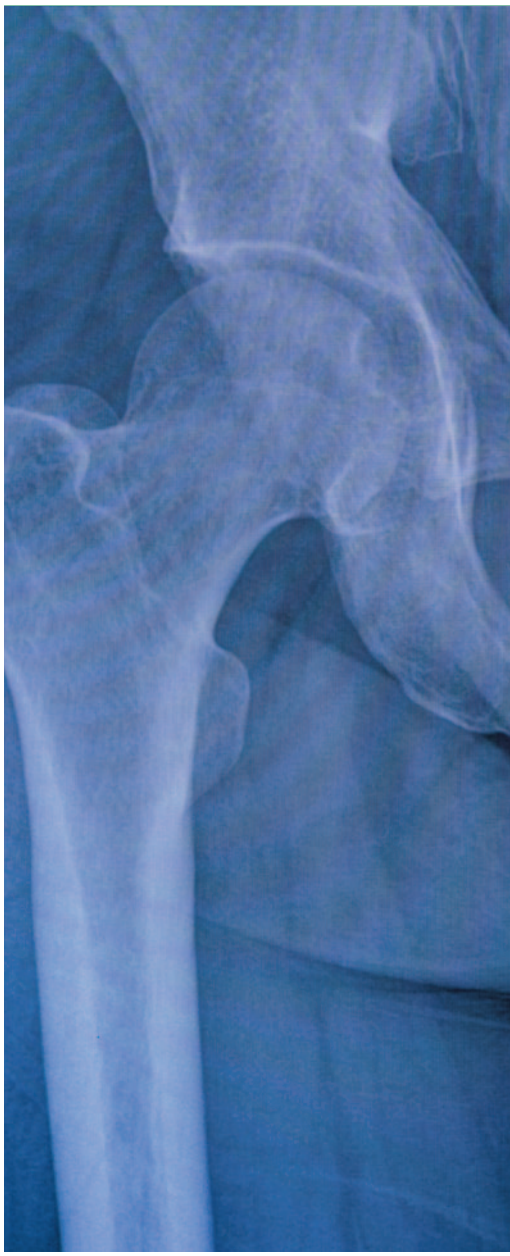
Clinical investigations for medical devices



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Abstract

This article focuses on the medical device specific aspects of clinical investigations and does not aim to be a comprehensive introduction to clinical trials. We highlight the key differences to clinical studies of medicinal products in the context of regulatory requirements in Europe, and discuss which documents are connected to the Clinical Investigation Plan. Finally, we discuss the different types of clinical investigations and the current status of the Clinical Investigation and Performance Studies module of EUDAMED (European Database for Medical Devices).

Introduction

Ten years ago, regulations governing the medical device industry were less strict than for the pharmaceutical industry, and clinical study documents for medical devices were mostly written by project managers. With the publication of the MedDev 2.7/1 Rev 4 guidelines on Clinical Evaluations[1] came greater stringency, and medical device companies became increasingly aware of the medical writing profession.[2] With the implementation of the new EU Medical Device Regulation 2017/745[3] (MDR) came an exponential increase in the demand for medical device writers, even if initially only for writing Clinical Evaluation Reports (CER). Meanwhile, many medical device companies have understood the added value of professional medical writers and now also enlist them to write Clinical Investigation Plans (CIP) and Clinicial Investigation Reports (CIR).

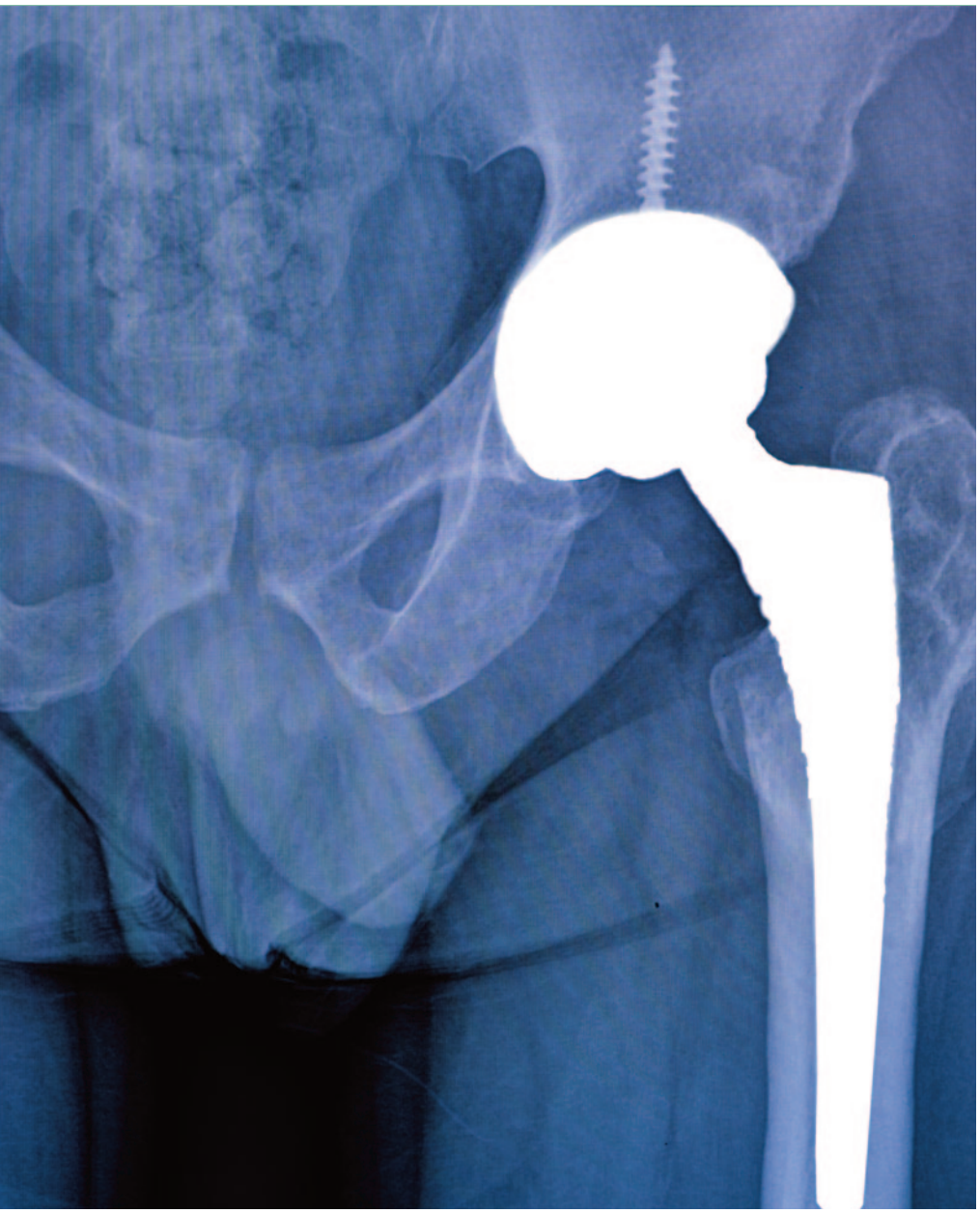
This article aims to familiarise writers with the medical device field and focuses on the medical device specific aspects of clinical investigations rather than broadly encompassing the subject of clinical trials. We further aim to provide a deeper understanding of clinical investigations for writers who work on other medical device documents to help them to put clinical investigation outcomes into context. We focus on Europe, but most aspects of this article are applicable to other regions as well.

Medical devices vs. medicinal products

In our opinion, the most relevant differences are as follows:

- Medical device trials are called "Clinical Investigations" rather than "Clinical Studies" or "Clinical Trials."
- There are no phase I trials in healthy volunteers. In low-risk class devices such as plasters, no clinical investigations are needed. In high-risk classes such as surgical implants, interventional procedures in healthy volunteers would be unethical.
- The clinical investigation design is associated with the risk class of the device. As mentioned above, a clinical investigation might not be necessary for devices classed as low risk. Previously, clinical data were often not needed for moderate-risk devices; though with the release of MDR 2017/745, there is an increasing requirement for clinical data for many such devices, which fosters the need for clinical investigations and hence the need for medical writers. However, the requirements in terms of clinical investigations are often less demanding than for high-risk class devices. Also, if a device is only temporarily used, the clinical investigation follow-up is usually only 30 days to cover procedure-related events, whereas for clinical trials with implantable devices, the follow-up period usually spans over several years.
- For completely novel devices with novel implantation techniques, it is difficult to know what to expect in terms of outcomes and complications, as data from animal studies are only partly translatable into clinical practice, and implantation techniques might be refined along the way.
- Another important difference is that the outcomes in clinical investigations are operator-dependent when an interventional or surgical procedure is involved. For instance, one can imagine that in the case of artificial hip joints, the success of the

> Outcomes in clinical investigations are operator-dependent.



intervention clearly depends on the surgeon. This should be borne in mind when designing, analysing, and interpreting a clinical investigation.

- Likewise, in the case of a novel surgical or interventional technique, there may be a learning curve involved. Consideration may therefore be given to the inclusion of roll-in patients in the CIP in such cases to cover at least part of the learning curve.
- With respect to the analysis of different populations, these are also more complex in the case of medical devices. Consider an investigation with an implantable device. What "what if" questions could be raised? In which group would a patient belong in whom the procedure was started but abandoned? In which group would a patient belong who had the device explanted? Would their follow-up be different from that of other patients?
- In contrast to pharmaceutical clinical trials, where an event is deemed as drug-related or not, an adverse effect that occurs in a patient with a medical device may be device-related or procedure-related. This is relevant since the device itself could work well, but the associated procedure could be too complicated for some surgeons. For example, when transfemoral transcatheter heart valves were developed, the initial antegrade access route was too complicated, so the procedure was adapted to use retrograde access instead.
- Also important is that device deficiencies may occur, which need to be recorded even if they did not necessarily result in adverse outcomes as they might have led to adverse outcomes if circumstances had been less fortunate.
- There are fewer possible interactions with the body in the case of medical devices compared to medicinal products that can interact with body systems at the molecular level. Consequently, clinical investigations of medical devices often need comparatively fewer patients.
- Blinding is more difficult in medical device investigations as the devices often differ in design, therefore often only single-blinded trials are possible, blinding the patients and eventually the core laboratory and clinical events committee to the treatment. Furthermore, placebo-controlled trials (sham procedures[4]) are very rare.
- Medical device companies are, on average, smaller than pharmaceutical companies. The effect of this difference is that the medical writer often has greater influence and more frequently contributes to strategic insights when writing the CIP for a medical device than when writing a Clinical Trial Protocol on behalf of a large pharmaceutical company with standardised document development and highly specialised roles.

For more details on the differences between writing for medical devices and medicinal products, please refer to the articles by Mallia and Walter[5] and Billiones and Thomas.[6]

Applicable regulations

Table 1 provides a non-exhaustive list of the main regulations and guidelines that are relevant for clinical investigations in Europe. In other regions, other regulations may apply such as the US 21 Code of Federal Regulations or Japan's Ministerial Ordinance on Good Clinical Practice for Medical Devices.

Documents related to clinical investigations

A CIP describes how a clinical investigation is conducted, the statistical analysis plan prespecifies the statistical analysis that will be performed, and the informed consent form summarises the clinical investigation for the patient. At the end of the clinical investigation or at specific time intervals, a CIR (final or interim

Table 1. Main regulations and guidelines relevant for clinical investigations in Europe

Declaration of Helsinki[6]	The Declaration of Helsinki is a set of ethical principles. It applies to medicinal products and medical devices.
ISO14155: 2020[7]	Clinical investigation of medical devices for human subjects - Good clinical practice. This ISO document is similar to ICH-GCP E6 for medicinal substances. Its annexes include content requirements for Clinical Investigation Plans, Clinical Investigation Reports, and Investigator's Brochures and provide an overview of different clinical investigation types.
MDR 2017/745[3]	European Medical Device Regulation that mainly describes how to bring medical devices to market and how to ensure their safety and performance. It provides details in terms of clinical investigations and its Annex XV is fully dedicated to clinical investigations.
MDCG guidance documents[8] **MEDDEV guidance**[9]	MDCG guidance documents are continuously developed (a regular check of the website is recommended), and supersede MEDDEV guidance documents. MDCG guidance documents cover several aspects of clinical investigations (application, modification, safety reporting), as well as the associated documents, such as Post-Market Follow-Up Plan and Report, etc.
Local regulations	Local regulations must also be respected, e.g. the Medical Device Act in Germany[10]
Disease specific guidelines, e.g., Academic Research Consortium guidelines[11]	Disease-specific guidelines shall also be respected when designing clinical investigations, e.g., for device trials in coronary interventions, the Academic Research Consortium guidelines provide harmonised definitions for endpoints in clinical investigations.

Abbreviations: ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practices; MDCG, Medical Device Coordination Group

report) is created. A beginners' guide to writing CIPs and CIRs for medical devices has been published recently by Jessica Norberg.[13]

The clinical investigation is an instrumental part of the clinical evaluation of the device (except for low-risk devices where a clinical investigation might not be necessary). It derives content from several other documents, and in turn becomes a reference for updates to those documents. The non-exhaustive Figure 1 below is a schematic representation of the documents that feed into and derive from clinical investigations; a brief description of these is provided in the glossary.

Types of clinical investigations

Before the release of ISO14155:2020,[8] the different types of clinical investigations were not clearly defined.[2] Annex I of this ISO guidance[8] covers this gap. It differentiates between **pre-market clinical investigations**, which are conducted with medical devices that have not yet gained market approval (CE-mark in Europe) and **post-market clinical investigations** (following market approval) as shown in Figure 2. For novel products in higher risk classes, first-in-human or feasibility studies may be necessary to gain initial information regarding the device's safety and to determine whether the procedure is feasible. These are comparable to phase II studies of medicinal products. Device or interventional modifications may be performed as necessary based on these studies, or new hypotheses will inform the design and sample size of pivotal clinical investigations, which are comparable to phase III trials of medicinal products. In the post-market phase, an investigation may be **interventional**, meaning an intervention occurs for the purpose of the investigation, e.g. additional x-ray assessments, or **non-interventional**, where the patients are treated according to the standard-of-care at the respective facility. **Company-sponsored** versus **investigator-initiated investigations**, and **prospective** investigations vs. **retrospective** analyses represent different approaches that are rather self-explanatory.

Trends in clinical investigation design

While clinical investigations were once fairly standard in the medical device field, there is a current trend towards new investigation designs, adapted from the ones used for medicinal products. Examples are **master protocols** that include a core protocol and sub protocols. Basket trials involve different patient populations, but the same product, and umbrella trials involve one patient population, but different products. The aim is to facilitate the creation of documents and their corresponding review by ethics committees and (if applicable) by competent authorities. Further details can be found in the article by Mackinnon and Gisbert.[14]

Another strategy is to combine different clinical investigation stages into one master protocol (e.g. pilot, pivotal and post market phase).

A novel, interesting, and efficient way of conducting randomised controlled trials is to "piggy-back" registries.[15] Furthermore, the concept of **adaptive trial design** is a strategy increasingly being used to make clinical investi-

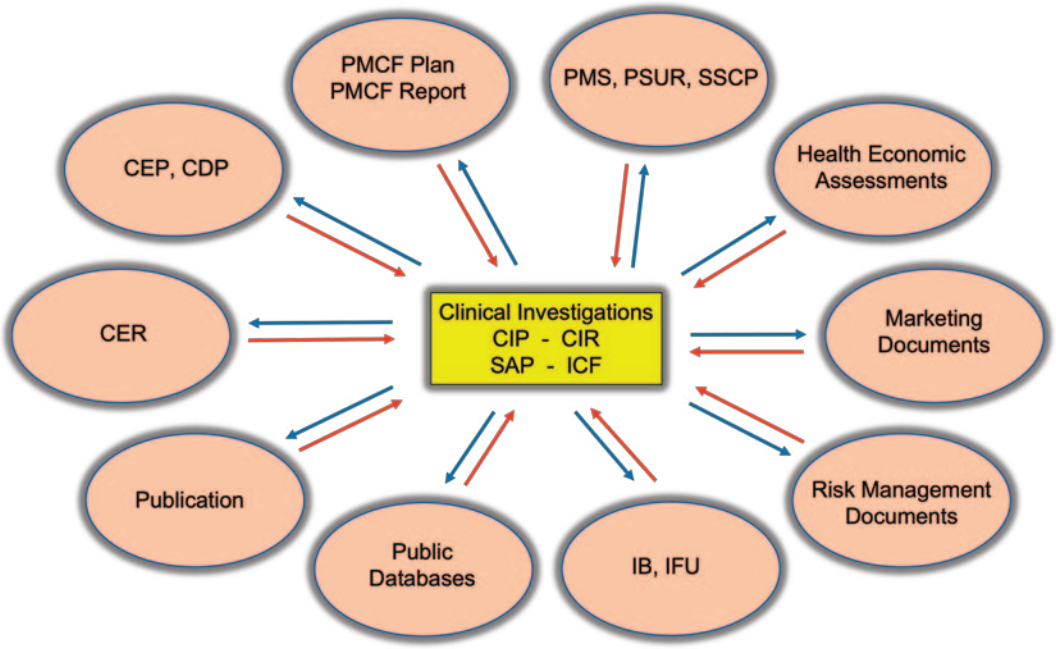


Figure 1. Documents associated with clinical investigations

Abbreviations: CDP, clinical development plan; CEP, clinical evaluation plan; CIP, clinical investigation plan; CIR, clinical investigation report; IB, investigator's brochure; ICF, informed consent form; IFU, instructions for use; PMCF, post-market clinical follow-up; PMS, post-market surveillance; PSUR, periodic safety update report; SAP, statistical analysis plan; SSCP, summary of safety and clinical performance

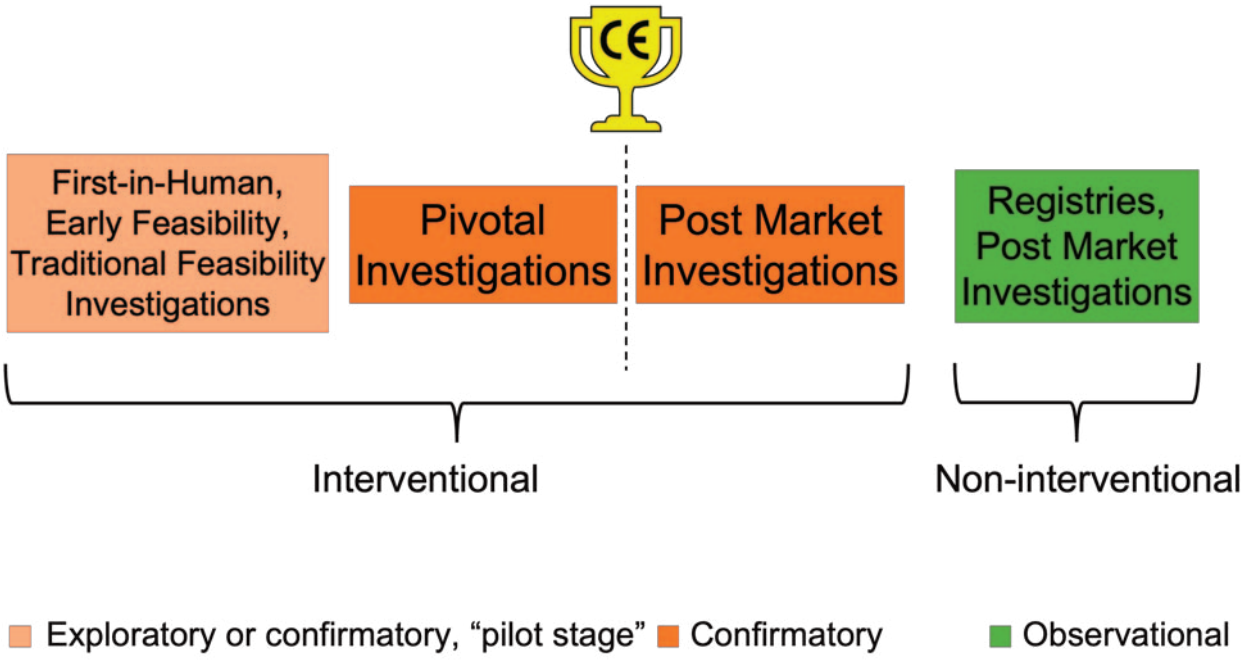


Figure 2. Clinical investigation types per ISO14155:2020[8]

gations more flexible and more efficient,[16] as well as **decentralised** trials.[17] New approaches are also being implemented for clinical investigation endpoints: While composite endpoints were routinely used in the past,[12] **hierarchical composite endpoints** are a new category defined by various disparate endpoints that are combined and are neither equivalent in severity nor assessed on the same scale.[18]

Lastly, and most importantly, as for medicinal products, **patient centricity** is becoming more important. The FDA released a statement to encourage patient engagement in medical device investigations and issued principles for Patient Reported Outcome Instruments for Use in medical device evaluations.[19,20]

EUDAMED

The European Database for Medical Devices (EUDAMED) is a multipurpose database created to address the need for greater transparency and traceability, as well as improved coordination of data related to medical devices that are marketed in the EU. It is composed of six modules, three of which are fully operational (Actor Registration, UDI Database and Registration of Devices, Certificates and Notified Bodies) and three of which are in various stages of readiness (Vigilance and Post-Market Surveillance, Clinical Investigation and Performance Studies [CIPS], and Market Surveillance).

The CIPS module will contain the key data from clinical investigations. Chapter 6, Article 73 of EU MDR 2017/745[3] stipulates that the user interface will be available in all official languages of the EU, and each clinical investigation will be assigned its own individual identification number. The sponsor will apply to conduct clinical investigations, follow up on them, report their results, and terminate them using this module. Serious adverse events and device deficiencies that arise during the course of the clinical investigation will be reported through the CIPS module. EU member states will be able to exchange certain sensitive information on clinical investigations that will be accessible only to EU member states and the Commission. Trial participants' personal information will not be accessible to the public.

Sponsors' confidential information, including the Investigator's Brochure and status of the device's conformity assessment, will not be accessible to the public unless there is an overriding public interest to disclose it. All other information, including the CIR, will be accessible to the public.

It is expected that all modules will be fully functional by Q2 2024. The first "Playground" launch date for the CIPS module was in mid-July 2022. The CIPS module is one of four whose use will become mandatory by the end of 2024, with the remaining two becoming mandatory by Q2 2026.[20] Notwithstanding, EUDAMED was originally scheduled to go live in May 2020, and delays have been announced three times thus far (Oct 2019, Oct 2021, and July 2022). Until EUDAMED is fully operational, MDCG 2021-1[9] provides guidance on alternative technical solutions.

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Conclusion

In summary, medical device clinical investigations have similarities and differences compared to clinical trials of medicinal products. Medical writers with experience in pharmaceutical clinical studies should be able to switch to medical device clinical investigations easily, bearing in mind the above-mentioned peculiarities. With the growing sophistication of medical device clinical investigations and relatively greater potential for input by the medical writer, writing CIPs and CIRs could offer an attractive path on which to embark.

Acknowledgement

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Disclosures and conflicts of interest

None.

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Glossary

The table below is a non-exhaustive list of documents that relate to clinical investigations. Further details are provided in the regulations and guidelines as specified in the section *Applicable Regulations*. Please note that not all documents are required for all medical devices, e.g. the Periodic Safety Update Report is only required for class IIa, IIb, and III devices, and the Summary of Safety and Clinical Performance only for class III and implantable devices.

Clinical Development Plan (CDP)	The CDP describes the clinical strategy of a device and is part of the Clinical Evaluation Plan (CEP). Clinical Investigations (CI) shall be conducted according to the CDP, but information obtained from the CI may also feed back to the CDP.
Clinical Evaluation Plan (CEP)	The clinical evaluation assesses clinical data of a device to verify its clinical safety and performance. The CEP plans the clinical evaluation and contains the CDP. Information obtained from the CI may feed back to the CEP (e.g. outcomes, areas that require further investigations).
Clinical Evaluation Report (CER)	The CER reports the outcomes of the clinical evaluation. CIs are an integral part of the CER, and Clinical Investigation Reports (CIR) are often attached to the CER. The CER may also feed into the CI, e.g. if gaps are identified that need to be covered through a CI.
Health Economic Assessment	Data from the CI may feed into the Health Economic Assessment. These might e.g. be Quality of Life questionnaires, length of hospital stay, operation time, etc. This is particularly relevant for novel devices for which reimbursement needs to be established.
Investigator's Brochure (IB)	The Investigator's Brochure summarises all preclinical and clinical data of a device. It is required for CIs with investigational devices. For CIs with an approved device, the Instructions For Use (IFU) usually suffices.
Instructions for Use (IFU)	The IFU is the packaging leaflet that describes how to use the device, how to store it, the potential complications associated with the device, etc. The IFU is required for CIs, but information obtained in CIs may also feed into the IFU, e.g. if new complications associated with the device have been identified.
Marketing documents	Marketing documents refer to communications to the public. This may be via websites, marketing brochures, etc. All clinical claims raised in these materials need to be substantiated with clinical data.
Post-Market Clinical Follow-Up (PMCF) plan	The PMCF plan specifies the collection and evaluation of clinical data. Even after a medical device gains market access (CE-mark in Europe), the manufacturer is frequently obliged to perform additional PMCF studies, e.g. with long-term follow-up, or to investigate the device in a larger group of patients to confirm the safety and performance of the device, or to register rare side-effects. The PMCF plan includes not only CIs, but also the screening of literature, etc. CIs shall be conducted according to the PMCF plan, but outcomes from CIs may also feed into the PMCF plan.
PMCF report	Amongst other PMCF activities, the PMCF report summarises the outcomes of PMCF CIs.
Post Market Surveillance plan (PMS)	Outcomes of CIs may feed into the post market surveillance plan and report (e.g. incidents).
Periodic Safety Update Report (PSUR)	The PSUR summarises the outcomes of the PMCF, but also contains data derived from other sources (e.g. complaint data).
Publication	The results of every CI should be published in a peer-reviewed journal. At least the outcomes must be made publicly accessible.
Entries in public databases	CIs need to be registered in public databases (for registries, it is recommended but not required). CIs will be registered in EUDAMED once the database is operational. Until then, the most commonly used database for trial registration is ClinicalTrials.gov.These databases may also contain the outcomes of CIs.
Summary of Safety and Clinical Performance (SSCP)	The SSCP provides an update on the safety and performance of the device and summarises clinical data. It shall be made available to the public (via EUDAMED once the database is live). Identified gaps may feed into the design of new CIs.
Risk management documents	Risk management documents feed into several other documents (e.g. the IFU) that have to be considered when writing a CIP, particularly in terms of risks, precautions, and warnings. Outcomes of CIs may likewise feed into risk management (e.g. event rates, new risks, new precautions).

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