

A beginner's guide to writing clinical investigation plans and reports for medical devices

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Abstract

A clinical investigation plan for a medical device must outline and justify all objectives of the clinical investigation, present and justify the investigational design and methodology, and state principal features of the statistical analysis. A clinical investigation report should summarise the plan, explain any deviations from it, and present and discuss the results of the clinical investigation. Preparing clinical investigational documents requires collaboration with numerous professionals with expertise in clinical practice, statistics, data management, monitoring, and regulatory requirements. While separate guidelines apply for medical devices and pharmaceuticals, with differences in terminology and safety reporting among other factors, they offer similar guidance on good clinical practice, adapted for the product type. As a medical writer, you should not be afraid to ask questions when things are unclear, or to offer input.

Due to recently implemented regulations for medical devices and in vitro diagnostics (IVD), the medical device industry is taking a major step towards the strictly regulated world of pharmaceuticals. Clinical data requirements for medical devices and IVD products have been sharpened considerably, and the previously feasible option of riding piggyback on clinical data from similar, marketed products has become very difficult.

Many legacy devices (i.e., existing CE-marked

devices) are therefore in a situation where they need to acquire more clinical data, sometimes complemented by slimming their device claims to limit the amount of data required. Devices not yet on the market need a plan to collect sufficient clinical data before applying for their CE mark. The market for compiling study documentation for the medical device industry is therefore booming. But how do you get started writing clinical investigation plans (CIPs) and reports (CIRs) if you have no previous experience from the medical device industry, or if you have no experience in writing clinical study documents at all?

Regulations

First, make sure to comply with applicable regulations, standards, and guidelines. In the EU, medical devices are regulated under the Medical Device Regulation (MDR),¹ IVD products under the In Vitro Diagnostics Regulation (IVDR),² and pharmaceuticals under the Clinical Trials Regulation (CTR).³ Medical device investigation protocols must follow the ISO 14155 standard for good clinical practice (GCP)⁴ and IVD study protocols the ISO 20916,⁵ whereas the pharmaceutical industry follows the International Conference on Harmonization guideline E6 (ICH E6).⁶

Always consider if other standards (e.g., product-specific) and national guidelines also apply. Although the EU is in the process of centralising guidance for collecting clinical data, the work is not complete and additional requirements may exist. In case of differences between standards, the most stringent requirements always apply. This article will focus on medical devices regulated by MDR¹ and ISO 14155.⁴

Terminology

Although the medical device industry is incorporating increasing vocabulary from the pharmaceutical industry, differences still exist. Some of the most important differences in terminology are presented in Table 1.

Clinical studies are divided into phase I to phase IV studies, whereas clinical investigations use a different terminology referring to pre- and post-market investigations, where pre-market clinical investigations are further divided into pilot stage or pivotal stage investigations.⁴

Before starting – understand where the clinical investigation puzzle piece will fit

When embarking on writing a CIP, start by reading the clinical evaluation plan (including the clinical development plan), clinical evaluation report, risk management report, and if available, the post-market clinical follow-up (PMCF) plan. If these have not been recently performed or updated, stop, and take a step back. They are essential building blocks laying the foundation for planning a clinical investigation, as described below. Ultimately, results from the completed investigation will be fed back into the PMCF report and into the risk analysis and clinical evaluation documents, which should be updated with the new clinical data, re-assessing their benefit-risk conclusions. This feed-back loop between risk

analysis, clinical evaluation, PMCF, and clinical investigations, is illustrated in Figure 1.

Clinical evaluation

A clinical evaluation is a requirement for all medical devices according to the MDR. During a clinical evaluation, pertinent data in relation to the device under evaluation and similar devices

A well-performed clinical evaluation identifies the need for a clinical investigation as well as appropriate endpoints, acceptance criteria, and investigational design, and hence lays the basis for planning a clinical investigation.

Table 1. Differences in terminology between the medical device and pharmaceutical industries

Medical device industry		Pharmaceuticals
Medical device	IVD medical device	Pharmaceuticals
Clinical investigation	Clinical performance study	Clinical study or clinical trial
Intervention	–	Treatment
Investigational medical device (IMD)	IVD medical device under investigation	Investigational medicinal product (IMP)
Performance or effectiveness	Performance	Efficacy
Investigational design	Clinical performance study design	Clinical study design
Clinical investigation plan (CIP)	Clinical performance study protocol (CPSP)	Clinical study protocol (CSP)
Clinical investigation report (CIR)	Clinical performance study report (CPSR)	Clinical study report (CSR)
Adverse device effect (ADE)	Adverse device effect (ADE)	Adverse drug reaction (ADR)

is identified through a systematic literature review, and by gathering manufacturer data. The state-of-the-art of the medical field is defined and the clinical data is appraised, analysed, and summarised in a clinical evaluation report. Potential gaps between existing data and data required by current regulations, are detected, and highlighted. In other words, a well-performed clinical evaluation identifies the need for a clinical investigation as well as appropriate endpoints, acceptance criteria, and investigational design, and hence lays the basis for planning a clinical investigation.^{1,7}

Risk analysis

Risks associated with the investigational medical device and any related clinical procedure should also be estimated when planning a clinical investigation, in accordance with ISO 14971.⁸ Residual risk according to an initial risk analysis, and risks to the subject related to the clinical procedure or required follow-up procedure, must be balanced against anticipated benefits. In simpler words, a risk-benefit balance must be achieved.⁴

The clinical investigation plan

The CIP is the key document of the clinical

investigation, and the basis of the application sent to the Ethics Committee (EC), and potential competent authority, for approval.

A CIP must clearly outline all objectives of the clinical investigation and justify them based on scientific and ethical principles.⁴ The CIP should present the investigational design and methodology, including details on intervention and control groups, number of visits, their timepoint and content, defined endpoints, and a rationale for the chosen design. A way to facilitate the understanding and presentation of the investigation is to include a schematic figure of the overall clinical investigational design.

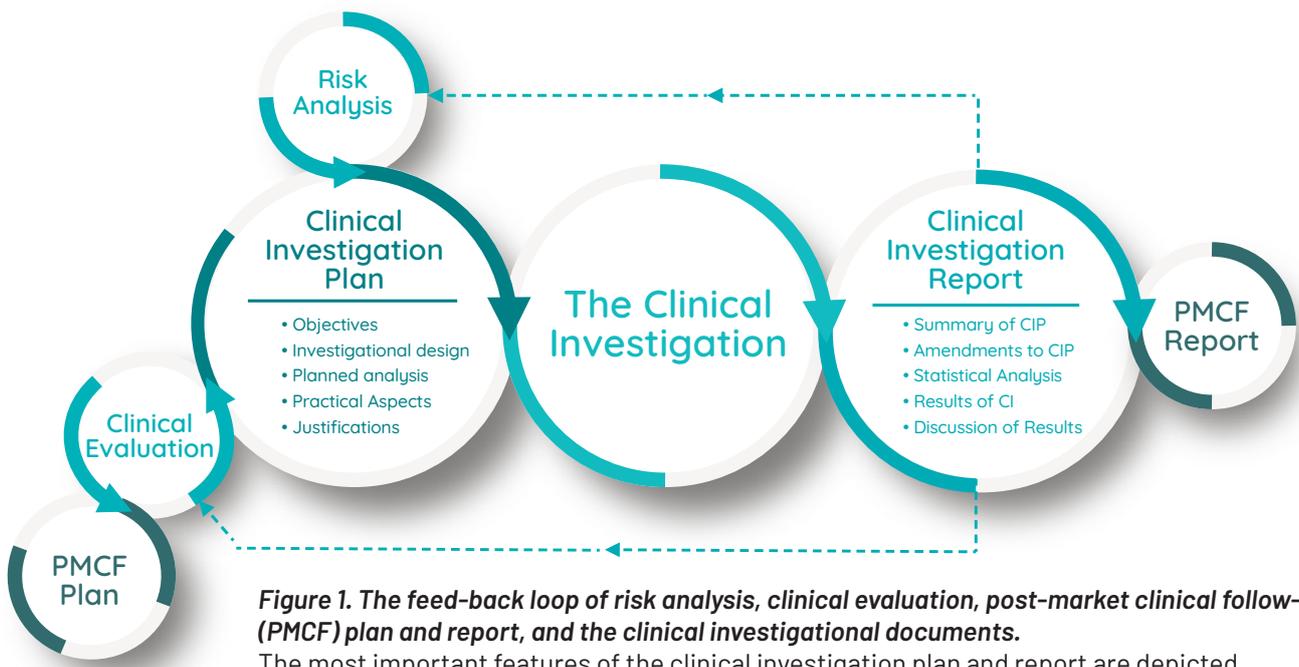


Figure 1. The feed-back loop of risk analysis, clinical evaluation, post-market clinical follow-up (PMCF) plan and report, and the clinical investigational documents.

The most important features of the clinical investigation plan and report are depicted.

Abbreviations: CI, clinical investigation; CIP, clinical investigation plan; PMCF, post-market clinical follow-up.

In Figure 2, an example of such an image from a fictional clinical investigation is presented. It is also common, and advisable, to include a table summarising the frequency and timing of clinical visits, and what will be done during each visit (e.g., procedures, lab tests, etc.). This table is called the schedule of events or schedule of activities, and is equivalent to the similar table that would be found in a clinical study protocol for an investigational medicinal product.

Principal features of the statistical analysis to be performed must be included in the CIP, as well as practical aspects such as the organisation, conduct, monitoring and record-keeping of the clinical investigation. For example, processes for how the informed consent shall be obtained, and how to capture data for each enrolled subject, should be specified. Importantly, all anticipated adverse device effects (i.e., adverse events related to the use of an investigational medical device) must be presented, together with a rationale for the related benefit-risk ratio.⁴

The coordinating investigator and the sponsor must sign off on the content of the CIP before the application is submitted. Principal investigators (PIs) for all participating sites, must agree to conduct the investigation accordingly, typically

by signing the final CIP (i.e., the version approved by the EC and competent authority). Any changes to the CIP after its approval, must be described in an amendment that must also be approved, if considered substantial.⁴

Consider keeping details out of the CIP

Although all information required by applicable regulations and guidelines should be present in a CIP, it's not always necessary to include a full description of this information, e.g., when it comes to data management, statistics, and monitoring. An option is to provide a short description in the CIP and refer to a separate document for details. This may save time and reduce costs, as these separate documents can be updated without affecting the CIP, thus reducing amendments, and approval rounds. Note however, that for less complex investigations it can be easier to keep everything in the CIP.

The clinical investigation report

Once the investigation is closed and the statistical analysis has been performed, it's time to write the CIR. A CIR is always required, even if the clinical investigation is terminated prematurely. The main goals of the CIR are to describe the clinical

investigation's design, conduct, statistical analysis, and results.⁴ In other words, the CIR should summarise the CIP, explain any deviations from it, and present and discuss the results of the clinical investigation. The discussion should include a critical appraisal of the results compared to stated objectives.⁴

The CIR must include data from all participating investigational sites so not to exclude any non-favourable data, and must never reveal subject identity. Ideally, all PIs should review the CIR. The final CIR requires signatures from the sponsor and coordinating investigator (or PI for single-centre investigations), before being made available to the EC and/or applicable regulatory authorities, depending on the country.⁴ The results from the clinical investigation should also be published in a publicly accessible database, and as mentioned above, should be used to update the risk analysis and clinical evaluation.

Differences between medical devices and pharmaceuticals

So, what then are the differences between writing study documentation for pharmaceuticals and medical devices? Well, except for the different guidelines and terminology already mentioned,

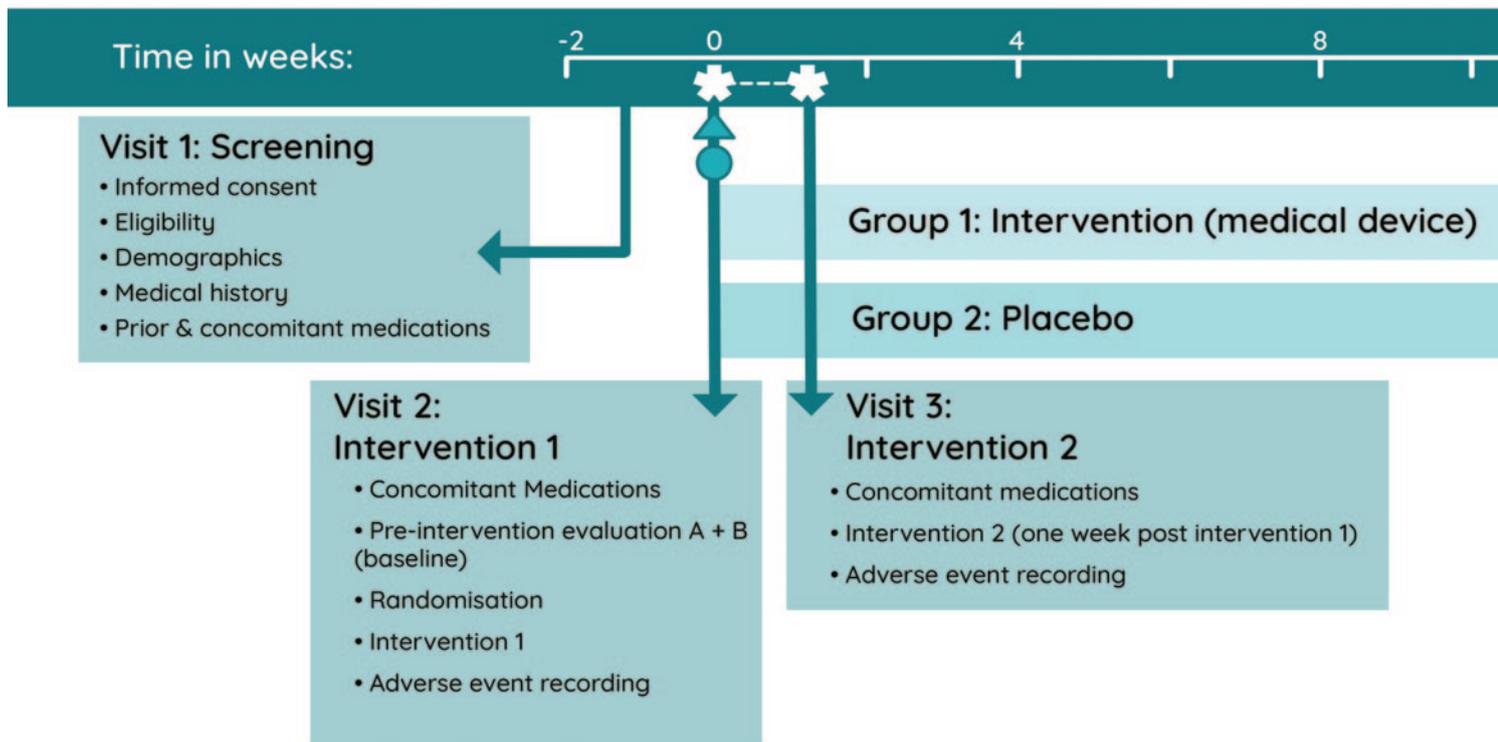


Figure 2. Overall clinical investigational design for a fictional clinical investigation.

Table 2. Important differences between study/investigational documentation

	Pharma	Medical devices
GCP guideline/standard:	ICH E6	ISO 14155 (medical device) ISO 20916 (IVD medical device)
Templates on study/investigational documents:	Mainly differences in structure and order of content	
Terminology:	Clinical study/trial, treatment, effect etc.	Clinical investigation, intervention, performance etc.
Safety reporting:	Differences in what to report and reporting timelines	

not that much. While separate guidelines apply, they offer similar guidance on GCP, adapted for each product type. Templates for clinical study/investigational documents provided in the guidelines also have a very similar content, although they have a different structure.

If you are preparing CIP and CIR templates from scratch, you can follow the order of the template offered in ISO 14155. If you already have a template according to ICH E6 (i.e., for a pharmaceutical product) you might use that as a basis, adjusting where needed to comply with regulations and guidelines for medical devices. Other sources for templates may depend on the country where the investigation is conducted,

e.g., the Swiss Association of Research Ethics Committees have published a CIP-template on the SwissEthics website.⁹ There is no regulatory requirement to present the content in a certain order, as long as all required information is provided. Table 2 summarises important differences between medical devices and pharmaceuticals to consider when writing study/investigational documents.

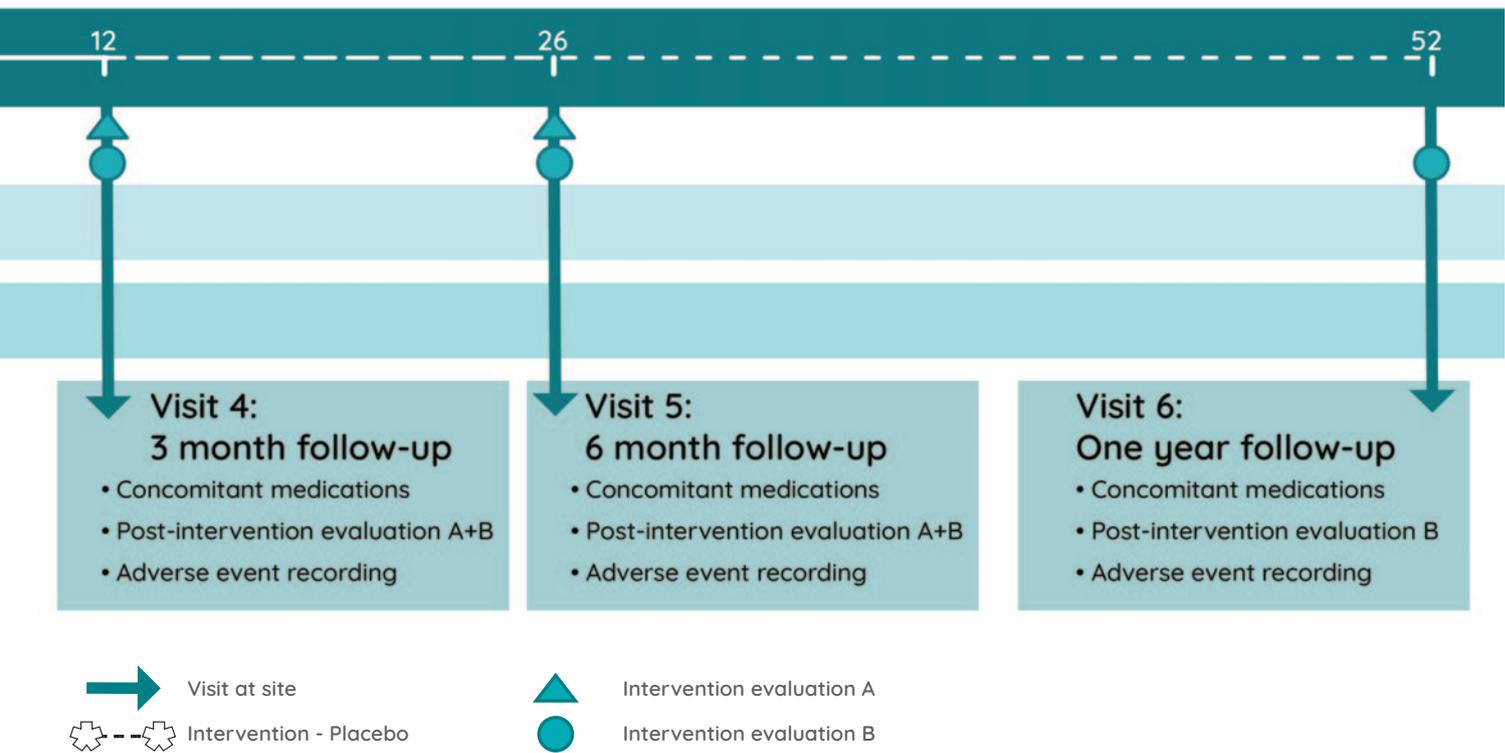
Risk assessment and reporting

Risk assessments are generally performed at an earlier stage and are in general more structured for medical devices than for pharmaceuticals, with more procedures around risks including

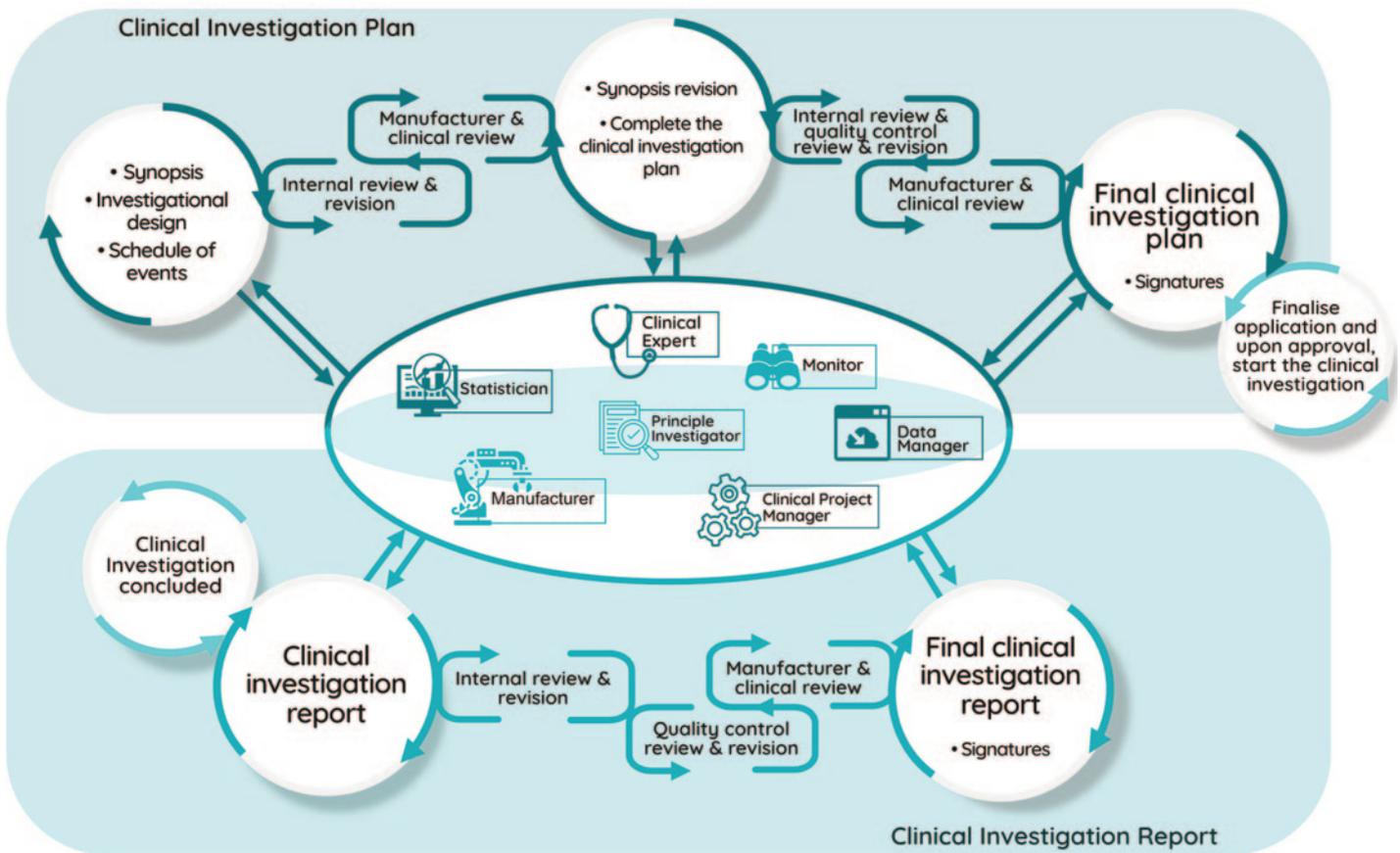
evaluation of residual risks. The requirements of what AEs must be reported, and within what timeframe, is an important difference between the two industries.^{4,6}

Clinical investigations may be less complex

Although not directly affecting the study/investigational documentation, it's good to be aware that clinical investigations are often less complex than clinical trials and more adapted to the type of product. In the pharmaceutical industry, a standardised set of studies are typically required, from phase I in a small number of healthy volunteers or in some cases severely ill



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Figure 3. Planning and collaboration example for writing CIPs and CIRs.

An example on how the planning for writing a CIP (upper panel) and a CIR (lower panel) could look like is depicted, as well as who you as a medical writer might collaborate with.

patients, to phase IV post-marketing studies. Clinical investigations are adapted depending on risk class and intended purpose, and one single clinical investigation may be sufficient if it provides clinical data that support all claims stated for the product.

Planning your work

When planning the writing to meet set deadlines, make sure to include enough time to get answers to your questions from the investigational team and experts, for reviews and revisions, and for juggling other projects on the side. No matter if you work at a consultancy company like me, freelance as a medical writer, or are employed by a manufacturer, it's good to involve the manufacturer, colleagues, and experts early in the drafting of a CIP. Exactly how this may look will vary depending on your work situation, experience, and specified assignment. An example of a plan for writing a CIP and CIR, and

who you might collaborate with, is depicted in Figure 3.

Start with the synopsis

When writing a CIP, I suggest to first prepare a draft of the synopsis and have that thoroughly reviewed before drafting the CIP in its entirety. This can save a lot of time by not needing to update the document in several places multiple times, as most questions and discussions will be in relation to the synopsis, and all content of the synopsis (the CIP summary) will appear also in the main document. Personally, I like to include the full section on investigational design in this first draft, including the figure on overall investigational design and the schedule of events

It's important to have the synopsis and investigational design, and later the full CIP, reviewed by people with various professions and expertise to catch potential problems with the plan as early as possible, and to ensure that the plan is practically feasible.

table. I do this since they often spark discussion and, together with the synopsis, they set the basis for the CIP.

It's teamwork

It's important to include the coordinating/ principal investigator and any other medical expert as early as possible when drafting the synopsis to

obtain input on clinical investigational design and study procedures, and to ensure an appropriate study setup as close to standard clinical practice as possible. Access to a medical expert with relevant knowledge for the investigation is required according to ISO 14155.⁴ The medical expert should be available to advise on the design of the investigation and to answer related medical

questions. Make sure to discuss any specific questions immediately with the clinician, or other concerned professionals (e.g., the investigation's statistician) or to discuss more general concerns with someone familiar with the project.

It's important to have the synopsis and investigational design, and later the full CIP, reviewed by people with various professions and expertise to catch potential problems with the plan as early as possible, and to ensure that the plan is practically feasible. If possible, to cover all theoretical and practical aspects, this should include a statistician, a monitor, and a data manager in addition to the clinical project manager, manufacturer, and the coordinating investigator. Depending on your own experience, you may also want to include someone more senior with regulatory knowledge.

Once the clinical investigation and the statistical report are finalised and you are ready to compile the CIR, make sure to clear out any questions regarding the statistical analysis with the statistician. While writing the CIR, you may also need to communicate with the data manager, monitor, and clinical project manager, depending on the project. The final CIR should be reviewed by the PIs and the manufacturer.

Your role as a medical writer

As already discussed, designing a clinical investigation and writing a CIP and CIR is a collaboration involving many professionals with various expertise. Everybody contributes with their knowledge, including you. As you will write the documents, it's crucial that you fully understand the objectives, endpoints, and methodology of the investigation. To do that you will need to communicate with people of other professions.

If you have written these types of documents before, either for pharmaceuticals or for medical devices, you will have gained experience in study design and can make a valuable contribution. But even if this is your first time writing a CIP or CIR, more than likely you still have valuable experience and a different perspective from the rest of the team that would be useful. Perhaps you have other medical writing experience, or experience from designing laboratory experiments, that can be applied. Hence, do not be afraid to suggest alterations or to ask questions when something is unclear. Your role as a medical writer may differ depending on your work

situation and requested support. Independently, you will be responsible for conveying the core ideas of the investigation, providing necessary information according to applicable regulations and guidelines, and for coordinating comments and creating consistency throughout the documents.

Conclusions

Writing CIPs and CIRs for medical devices is not very different from preparing corresponding documentation for the pharmaceutical industry. The most important is to follow applicable guidelines, use correct terminology, and be aware of certain differences such as safety reporting and its timelines. To get started writing CIPs and CIRs, read up on applicable guidelines, start with the synopsis, believe in your abilities, and don't be afraid to ask questions and provide input. Remember, preparing study documents is a collaboration.

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Disclaimers

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

Disclosures and conflicts of interest

The author declares no conflict of interest.

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