EBOOK

Ultimate Guide to ISO 14155:2020 for Medical Devices

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Clinical investigations play an important role in the journey of bringing a medical device to market.

And while clinical investigations are often seen as difficult and complicated—often overwhelmingly so—a firm understanding of the relevant standards can go a long way to demystifying the process.

The most important standard to know and understand, ISO 14155:2020, is a guide to good clinical practices for the clinical investigation of medical devices for human subjects.

In this eBook, I'm going to give you an overview of the standard and Good Clinical Practices (GCP), and then walk you through some of the most important aspects of planning and conducting a clinical investigation in compliance with ISO 14155:2020.

(**A note on terminology**: "Clinical investigation", "clinical trial", and "clinical study" are all synonymous, and I'll be using them interchangeably..)

What is ISO 14155?

ISO 14155:2020 provides the general specifications and requirements for clinical investigations of medical devices. The latest version of the standard was published in 2020 and is intended to serve as a guide for clinical research professionals during the design, conduct, recording, and reporting of clinical trials related to the safety and effectiveness of medical devices.

The purpose of ISO 14155 is to:

- Protect the rights, safety, and well-being of human subjects;
- Ensure scientific conduct of the clinical investigation and credibility of the clinical investigation results;
- Define the responsibilities of the sponsor and principal investigator;
- Assist sponsors, investigators, ethics committees, regulatory authorities, and other bodies involved in the conformity assessment of medical devices.

The latest version of the standard is ISO 14155:2020, and it contains several updates from the older version of the standard.

What's new in the 2020 edition of ISO 14155?

The biggest difference between the ISO 14155:2020 and ISO 14155:2011 is the 2020 version's emphasis on the application of risk management principles throughout the entire clinical investigation process.

Annex H of ISO 14155 (*Application of ISO 14971 to clinical investigations*) explicitly lays out the connection between ISO 14971 and the clinical investigation process. It includes a helpful graphic for applying ISO 14971 to the management of potential safety concerns during a clinical investigation.

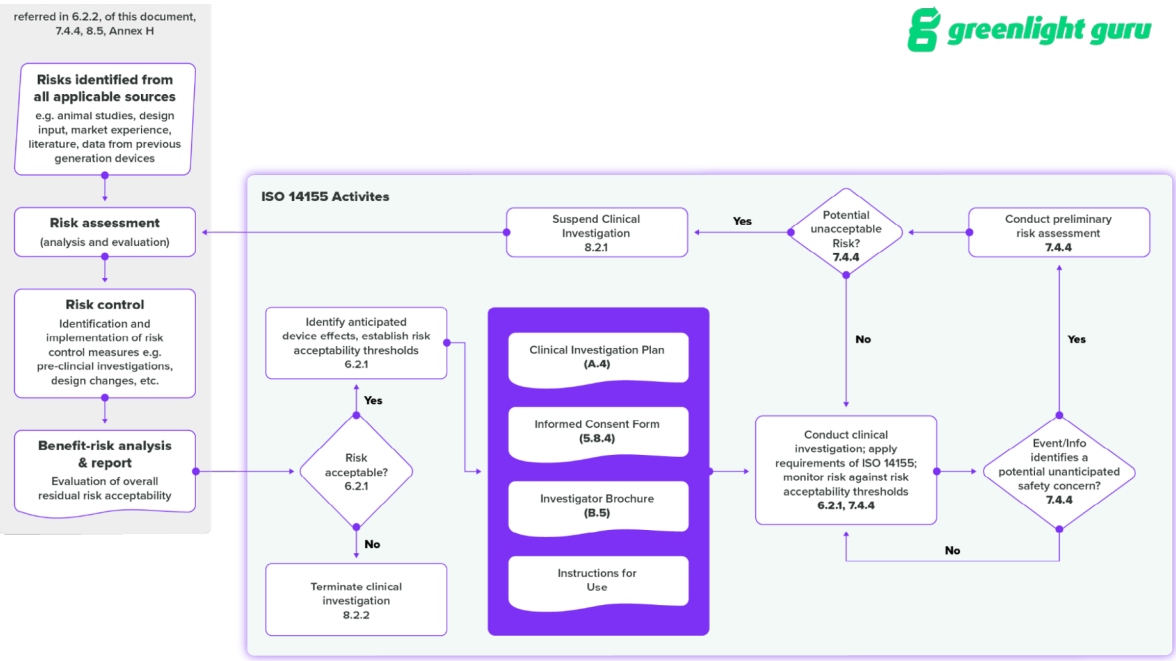


Figure H.1–Application of ISO 14971 to the management of potential safety concerns in a clinical investigation

There are other important changes to the 2020 version of the standard, as well, including:

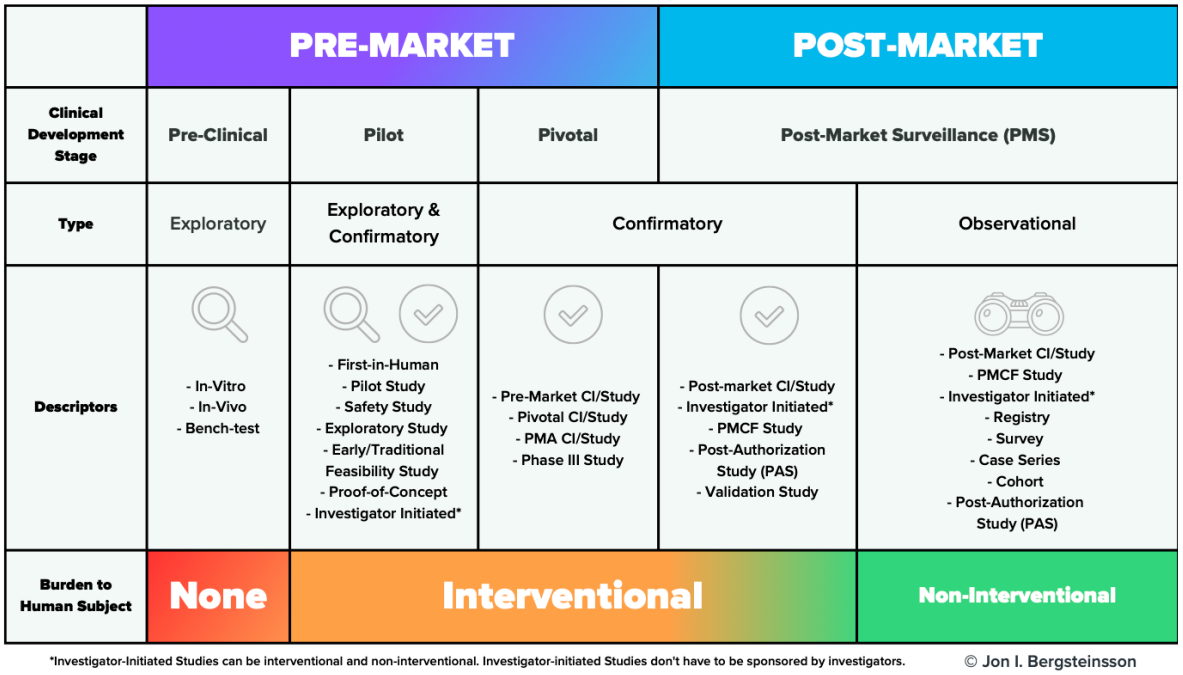
- A summary of Good Clinical Practice (GCP) principles in Section 4
- Requirement for the registration of all clinical investigations in a publicly accessible database like EUDAMED

- The inclusion of clinical quality management in section 9.1
- The inclusion of statistical considerations in Annex A
- Additional guidance for ethics committees in Annex G
- Requirements for risk-based monitoring in Section 6.7
- Guidance on clinical investigation audits in Annex J
- Guidance on the application of ISO 14155 in pre- and post-market stages in Annex I

What is the applicability of ISO 14155 in post-market clinical activities?

There are numerous types of clinical investigations, and the different language used to describe them can quickly become confusing. On top of that, clinical activities can occur at any stage in the product lifecycle, from pre-market to post-market.

The previous version of ISO 14155 did not do a great job of explaining how the standard applied to different types of clinical investigations at different stages in the product lifecycle. The standard writers have attempted to clear up some of this confusion in ISO 14155:2020 with the addition of Annex I, which clarifies the different types of clinical investigations based on regulatory status, clinical development stage, study design, and burden to subject.



As this image makes clear, clinical investigations don't just happen in the pre-market phase. ISO 14155 applies to post-market clinical investigations as well, including observational (non-interventional) investigations.

Which parts of ISO 14155 will apply to your clinical investigation?

In addition to the clarification of the different types of clinical investigations, Annex I also includes a section (I.7) on the applicability of the document's principles to different clinical investigations.

As the standard states: "Depending on the clinical development stage and the type of clinical investigation design, the principles of this document can be applied in full or in part."

For example, the standard states that for a pre-market confirmatory (interventional) clinical investigation, "all principles in this document apply." On the other hand, if you're undertaking a post-market observational investigation—which is non-interventional—you may not be required to apply every requirement in ISO 14155.

The important thing to remember is that if you believe you are exempt from applying any part of this standard to your clinical investigation, you must justify that decision in your clinical investigation plan (CIP).

What is Good Clinical Practice (GCP)?

Good Clinical Practice (GCP) is a set of ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve human subjects. GCP is an internationally recognized standard, and ensures that the rights, safety, and well-being of subjects are protected and that all clinical data is credible.

ISO 14155 provides a summary of GCP principles in Section 4 of the standard. These principles are critical requirements for carrying out any research involving human subjects and are the foundation of any good clinical investigation.

Overall, there are 14 guiding principles of Good Clinical Practice, including:

- All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols
- The benefits of conducting trials should outweigh the risks
- The rights, safety and well-being of trial participants are of paramount importance and these should be preserved by obtaining informed consent and maintaining confidentiality
- The care must be given by appropriately qualified personnel with adequate experience
- Records should be easily accessible and retrievable for accurate reporting, verification and interpretation
- Investigational products should be manufactured according to Good Manufacturing Practice

You'll want to familiarize yourself with all the principles laid out in Section 4 of ISO 14155, as they are essential to planning and conducting an ISO 14155-compliant clinical investigation.

In fact, in the Ethical Considerations portion of the standard (Section 5), the first requirement states that the Good Clinical Practices "shall be understood, observed, and applied at every step in the clinical investigation."

Section 5 also lays out several other important ethical considerations, including:

- Rules against improper influence or inducement of subjects
- Requirements for communication with the ethics committee (EC), including requirements for your initial submission and continuing communication throughout the clinical investigation.
- Requirements for obtaining informed consent and the information that must be provided to the subject. This section is particularly in-depth, as getting informed consent appropriately is critical to conducting an ethical clinical investigation in accordance with GCP.

What are the key responsibilities of the sponsor and principal investigator during a clinical investigation?

ISO 14155 separates the good clinical practices for 'Responsibilities' into two clauses, Responsibilities of the Sponsor (Clause 8) and Responsibilities of the Principal Investigator (Clause 9).

The sponsor (in our case, the manufacturer of the device) is responsible for planning and conducting the clinical investigation within prescribed quality assurance and quality control principles. It's important to note that even if the clinical investigation is contracted out by the sponsor to a qualified third party, the sponsor still retains overall responsibility.

The responsibilities of the Principal Investigator include: the implementation and management of the day-to-day activities of the investigation in accordance with the CIP, ensuring the integrity of investigation data, and safeguarding the rights, safety and well-being of the human subjects involved in the study.

How to plan a clinical investigation according to ISO 14155

As you plan your clinical investigation, it's important to understand that a standard like ISO 14155 is not telling you exactly what to do. It's telling you what you need to include and consider as you plan your clinical investigation.

Going through the standard and making sure you've checked off boxes and created all the appropriate documents is important, but it's not the end of your work. Regulatory authorities will want to see the justification for your decisions. They'll want to know why you've decided to structure your study a certain way, why you've chosen that sample size, or how you came up with a specific number. Section 6.3 (Justification for the design of the clinical investigation) has more information on providing that justification.

Keep that in mind as you build out the various documents that you'll need to create in the planning stage, which include:

- **The Clinical Investigation Plan (CIP)**. The CIP is the go-to document for everyone involved in the clinical study. It will include the objectives and design of your clinical study, as well a justification of the study's design, and a benefit-risk analysis. You can find the full list of what to include in your CIP in **Annex A** of ISO 14155:2020.
- **The Investigator's Brochure (IB)**. The purpose of the IB is to provide the principal investigator with sufficient data to justify the clinical investigation proposed in the CIP. The IB will include a summary of all the preclinical testing performed on the investigational device, as well as any existing clinical data. You can find the full list of what to include in the IB in **Annex B** of ISO 14155:2020.

- **Case Report Forms (CRFs)**. The purpose of CRFs is to provide information on the condition of each subject entering the study and to then capture data for each subject as required by the CIP. You can find the full list of what should be included in a CRF in **Annex C** of ISO 14155:2020.

Now, that basic description of CRFs is deceptively simple. Case report forms are one of the critical methods of collecting clinical data during a study, and using paper or clunky general-purpose software for your CRFs puts you at a high risk of missing data or slowing down your study with data entry mistakes.

At Greenlight Guru, our modern eCRF is built for the unique needs of the MedTech industry. When you use Greenlight Guru Clinical, you can get started in no time and ensure peace of mind with our pre-validated software, regulatory templates, and user-friendly study builder.

How to conduct a clinical investigation in accordance with ISO 14155

Your clinical investigation may only commence once you have “written approval/ favorable opinion” from the ethics committee and the relevant regulatory authority in the countries where your clinical investigation is taking place.

You’ll find requirements for conducting an ISO 14155-compliant clinical investigation in Section 7 of the standard, and there are a couple points within this section that I want to highlight here.

First, you’ll notice that a large part of Section 7 is given over to adverse events and device deficiencies. Documentation and reporting of adverse events or device deficiencies is extremely important, and you can find a table for adverse event categorization in Annex F of ISO 14155.

Fortunately, Greenlight Guru Clinical offers an adverse event module for EU MDR and ISO 14155-compliant reporting. The customizable module is fully

integrated into our eCRF and provides automatic notifications to users and sponsors and an AE specific data export.

Managing risks during a clinical investigation

Section 7 of ISO 14155 also touches on risk management—specifically, the risk assessment process for potentially unacceptable risks in 7.4.4. This subsection addresses risks that arise during the clinical investigation, and it provides a written version of the flowchart found in figure H.1.

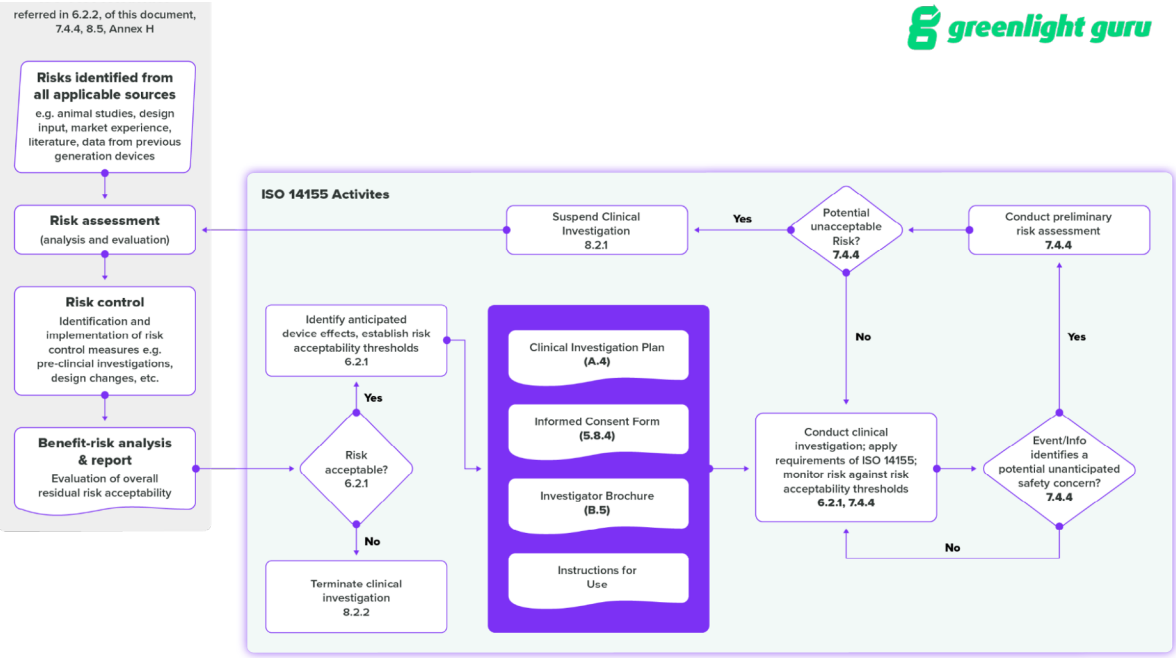


Figure H.1–Application of ISO 14971 to the management of potential safety concerns in a clinical investigation

Section 7 isn't the only place that risk management is mentioned in the standard, however. Section 6.2 (Risk management) provides more risk management requirements for clinical investigations.

Here, the standard states that risk management activities “shall be performed throughout the clinical investigation” and that risk management principles must be applied during both the planning and the conduct of the investigation.

The emphasis here on using ISO 14971 and applying risk management principles throughout the clinical investigation is part of a larger, industry-wide move toward integrating risk management into every part of the medical device lifecycle.

Taking this kind of holistic approach to risk means you may even want to document risk management for clinical investigations within your quality management system. Your risk management activities during a Post-Market Clinical Follow-Up investigation, for example, may have implications for your device that should be documented and fully traceable in your QMS.

At Greenlight Guru, we understand that risk is a fundamental part of bringing a medical device to market. That’s why we built our Risk Management workspace to be fully traceable with the rest of our QMS and compliant with ISO 14971:2019 and the risk-based requirements of ISO 13485:2016.

Electronic data capture and compliance with ISO 14155:2020

You’ll also want to pay close attention to Section 7.8 (Document and data control), especially Section 7.8.3, which covers electronic clinical data systems.

If you’re using an electronic data capture (EDC) system for clinical data collection during your study, you should know that ISO 14155 requires any electronic system be validated “in order to evaluate the authenticity, accuracy, reliability, and consistent intended performance of the data system.”

The standard follows that up with a list of 12 written procedures that must be implemented with the use of any EDC system. These include requirements to:

- Verify and validate that the requirements for the electronic clinical data system can be consistently met
- Ensure attributability, completeness, reliability, consistency, and logic of the data entered
- Ensure that data changes are documented and an audit trail is maintained
- Maintain a security system to prevent unauthorized use of data, both internally and externally

And while that may seem daunting, with Greenlight Guru Clinical, you'll have a system that comes pre-validated to all the requirements in ISO 14155:2020. That includes out-of-the-box compliance with the requirements in Section 7.8.3 and a suite of compliance document templates available to all customers.

Final thoughts: Greenlight Guru Clinical is pre-validated for MedTech data collection requirements

Planning and Conducting an ISO 14155-compliant clinical investigation is difficult enough without having to worry about your data collection tools.

That's why we built Greenlight Guru Clinical specifically for the needs of the MedTech industry. As the leading clinical data collection toolbox for MedTech, Greenlight Guru Clinical allows you to collect and manage clinical data in pre and post-market clinical studies, including registries, cohorts, surveys, human factor testing, design validation, and more.

Our solution meets the regulatory requirements of the FDA, EU, and most other countries, and ensures compliance out-of-the-box with GCP and ISO 14155:2020.

Get your free demo of Greenlight Guru Clinical today!

Clinical Data Collection Toolbox Designed for MedTech Studies

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