WHITE PAPER PRESENTED BY PREMIER RESEARCH

Applying Sound Research Practices in the Development of Medical Devices

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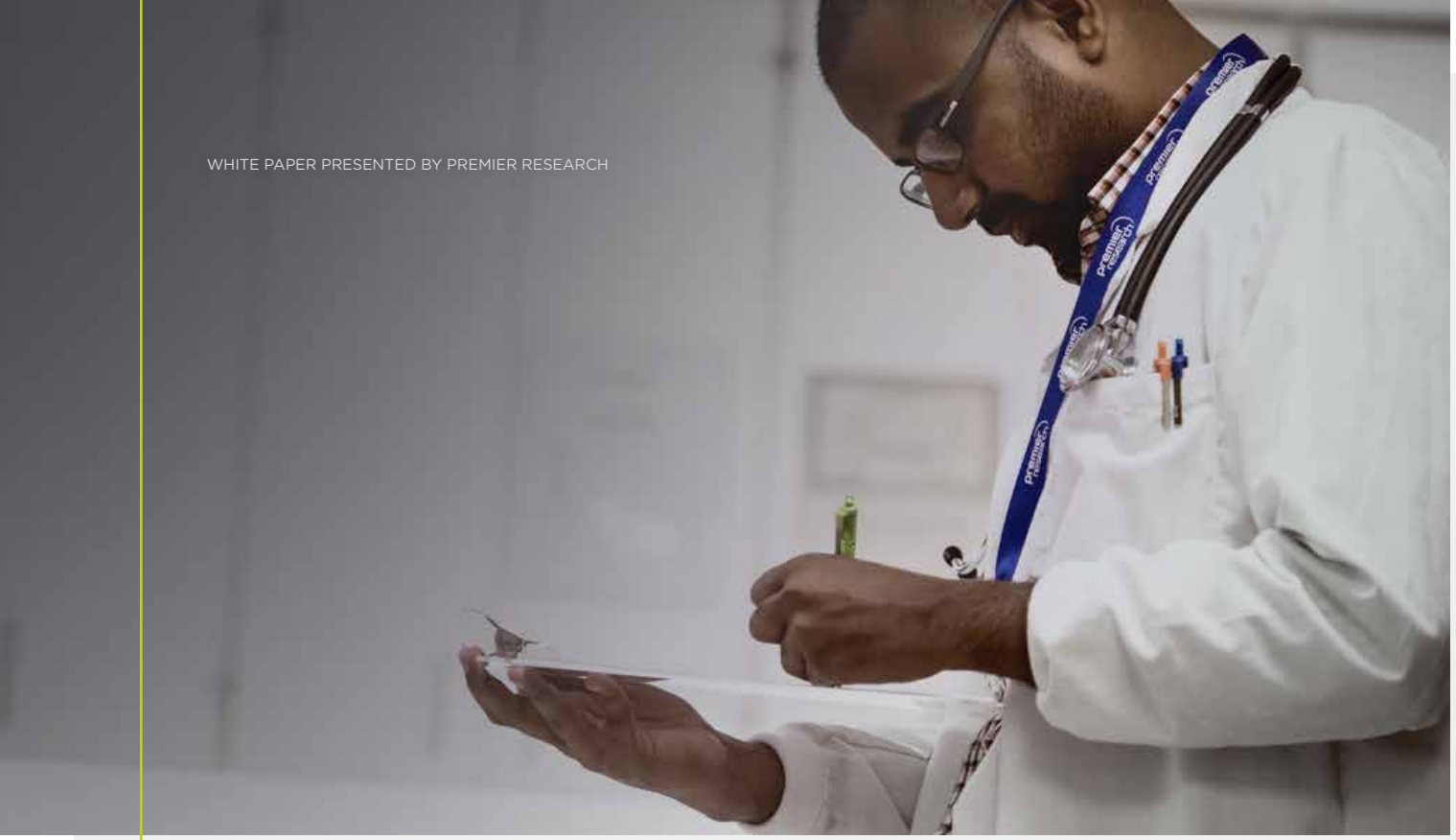
ABSTRACT

Medical device and diagnostic companies face greater demand to provide clinical evidence of product efficacy than ever before. With increased scrutiny from regulators, healthcare systems, and even patients, more device companies are performing clinical trials to improve the likelihood of commercial success.

MEDICAL DEVICE



Introduction

In today's competitive landscape, device companies are facing increased demand for clinical evidence of product efficacy and safety. In addition to pressure from regulators prior to market approval, device companies must answer to other stakeholders, including:

+ Payers who are requiring more information to substantiate product value claims to approve reimbursement
+ Physicians and healthcare systems who are requesting more evidence to inform purchasing decisions
+ Patients who are asking for increased transparency into the development process

This increased scrutiny has prompted more device companies to perform clinical trials to meet regulatory requirements, differentiate their products, and position their products for earlier adoption and success in the market.

Medical device trials must be designed to verify the performance characteristics defined by the manufacturer, determine undesirable side effects under normal conditions of use, and allow an informed assessment of the risk-to-benefit ratio in relation to the intended performance of the device. ISO 14155:2011 sets the international standard for good clinical practice in medical device trials, and a thorough understanding of these guidelines will help sponsors design and conduct studies that stand up to regulatory scrutiny. In this white paper, we examine best practices for the conduct of medical device clinical trials, the principles of which are defined in ISO 14155:2011.

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A global standard for good clinical practice in device trials

Sound research practices are the backbone of any rigorously-conducted clinical investigation. ISO 14155:2011 addresses good clinical practice for the design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.[1] While ISO 14155:2011 has similarities to the ICH standards for good clinical practice, it is more current and addresses issues that are unique to the evaluation of medical devices.

ISO 14155:2011 specifies general requirements intended to:[1]

+ Protect the rights, safety, and well-being of human subjects
+ Ensure the scientific conduct of clinical investigations and the credibility of the 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

Of note, ISO 14155:2011 does not apply to in vitro diagnostic medical devices.

ISO 14155:2011 has been widely adopted as the standard for medical device clinical trials, and global conformity to this standard will help to harmonize good clinical practices and ensure the reliability and integrity of the data submitted to support any marketing application, while ensuring that patients are protected. Sponsors are strongly recommended to follow ISO 14155:2011 as an increasing number of regulatory agencies and notified bodies are utilizing this standard for device assessment. While ISO 14155:2011 is not part of the official U.S. Food and Drug Administration (FDA) regulatory requirements for medical devices, the FDA recognizes the principles it represents. The principles set forth in ISO 14155:2011 also apply to investigations for non-regulatory purposes and should be followed as far as possible.

Ethical considerations for medical device trials

ISO 14155:2011 indicates that clinical investigations should be conducted in accordance with the ethical principles originating in the Declaration of Helsinki, which place the rights, safety, and well-being of human subjects over the interests of science and society.

As with any clinical study, there are a variety of ethical considerations that must be taken into account in medical device trials:[1]

+ Study design – The study must be designed in such a way that Ethics Committees can not only understand the purpose, design, benefits, and risks of the study, but also determine that there will be fair redress if the subject suffers from an adverse event as a result of study participation
+ Methods of recruitment – The sponsor must avoid improper influence on, or inducement of subjects
+ Informed consent – The informed consent form should be clearly written in non-technical language, so patients can understand what is expected of them
+ Data protection
+ Institutional Review Board/ Independent Ethics Committee (IRB/IEC) approvals and any updates that need to be made
+ Payments to subjects/investigators, incentives, and conflicts of interest – Compensating subjects for costs resulting from participation in the study may be appropriate if allowed by national regulations, but compensation should be not so large as to unduly encourage subjects to participate
+ Insurance and indemnity

+ Special populations – This may include subjects who lack the capacity for informed decision-making (e.g., patients in emergency situations, mentally ill patients, or pediatric patients) or subjects who have no alternative treatment options available to them. There are added ethical dilemmas associated with these groups, and measures must be taken to ensure that these subjects are protected. According to ISO 14155:2011, studies should only be conducted in vulnerable populations when they cannot be carried out in non-vulnerable populations.

A favorable opinion from a relevant IRB/IEC is required before proceeding with a device trial. Exceptions to this rule are proof-of-concept studies where assignment of patients to a particular therapeutic strategy or diagnostic procedure is not defined in advance in the protocol and where there are no diagnostic or monitoring procedures that fall outside of usual clinical practice.

Evaluating study design

Medical device studies must be designed to show both clinical and statistical significance. Designing studies to collect the right data is far more important than simply collecting more data.

Two important factors to consider when designing a medical device study are:

1. Bias – Bias can be introduced not only in the study design but also by subject selection, study conduct, and data analysis. Clearly, study designs that eliminate or reduce bias are preferable, as they minimize the risk that bias will invalidate study results.

2. Variability – Sampling variability is another general consideration in study design. Variability can be controlled or reduced by a more efficient design or by a larger sample size. However, it is important to note that a larger sample size will not necessarily address the issue of bias.

In 2013, the FDA issued a guidance document, *Design Considerations for Pivotal Clinical Investigations for Medical Devices*, which provides guidance to those involved in designing clinical studies intended to support pre-market submissions for medical devices and FDA staff who review those submissions. In this document, the FDA describes different clinical study design principles and defines how a sponsor should decide which pivotal clinical study design should be used to support a submission for a particular device.[2]

Selecting investigators, sites, and subjects

Choosing the best investigators and sites to engage the right subjects — especially when studying small populations — is fundamental to successful device trials.

Under ISO 14155:2011, investigator selection is the responsibility of the sponsor. Investigators should not only have therapeutic area experience and the necessary technical expertise, but also be familiar with the principles of good clinical practice.

Figure 1. Sample criteria for evaluating clinical trial sites

- Is the site experienced with medical device trials for the indication under investigation?
- Does the site have the patient population to support the study?
- Is there high staff turnover?
- Are there sufficient resources to conduct the clinical trial?
- Can the Principal Investigator provide a dedicated study coordinator?
- Will the site staff be able to meet your training needs throughout the duration of the study?
- For teaching institutions, will resident physicians be staffed on the clinical study, or will they be rotated on and off the trial by the PI?

When selecting sites, sponsors should remember that sites should be representative of the types of sites where the device is intended to be used. Similarly, study patients should be representative of the target population to minimize selection bias. Study patients should also reflect the target condition spectrum. If they do not, estimates of diagnostic clinical performance may be subject to spectrum effect.

As recruitment is a common hurdle in any clinical trial, sponsors should ensure that there are no competing studies that could delay their investigation. Under ISO 14155:2011, it is the responsibility of the principal investigator (PI) to ensure that he or she has the required number of eligible subjects needed within the agreed-upon recruitment period.

Getting it right: study start-up

It is extremely important to get an investigation right from the start. First patient first visit is often used as a metric for study start-up, but it is not a good metric from a quality perspective. Instead, sponsors should allow sufficient time to:

+ Write a good Clinical Investigational Plan
+ Develop well-written Informed Consent Forms
+ Ensure relevant insurance and indemnity are in place
+ Document compensation and confirm that it complies with local regulation
+ Obtain regulatory, IRB/IEC, and other country-specific approvals (Note: If national or regional ethics requirements are less strict than ISO 14155:2011, then the sponsor should apply the more stringent requirement)
+ Put study plans (e.g., monitoring, safety reporting, and data management) in place prior to patient recruitment
+ Obtain translations of necessary study documents, as defined by local or national law or the sponsor's standard operating procedures
+ Establish a Data Monitoring Committee
+ Ensure contracts are in place with qualified vendors and sites/PIs
+ Define and document procedures for issue escalation and resolution

Developing a Clinical Investigational Plan

The Clinical Investigational Plan (CIP) provides the absolute standard for defining the study population and ensuring subject safety. Generally, the CIP states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct, and record keeping of the study.

ISO 14155:2011 provides detailed information on the topics that should be included in the CIP.

Per ISO 14155:2011, the CIP must be approved, signed, and complied with by the PI. To help ensure compliance, sponsors should also develop an implementation plan for the CIP and a process for informing investigators and sites of any changes to the CIP. In some instances, regulatory approval of changes to the CIP may be required.

Figure 2. Content of a Clinical Investigational Plan[1]

General information
- + Introduction
- + Identification of the CIP
- + Sponsor information
- + Principal investigator, coordinating investigator, and investigation site(s)
- + Overall synopsis of the clinical investigation

Identification and description of the device

Justification for study design

Risks and benefits
- + Anticipated clinical benefits and adverse effects
- + Risks associated with study participation
- + Possible interactions with concomitant medical treatments
- + Steps that will be taken to control or mitigate risks
- + Risk-to-benefit rationale

Study objectives and hypotheses

Study design
- + Description of study design
- + Description of measures to be taken to minimize bias
- + Endpoints, with rationale for their selection and measurement
- + Inclusion and exclusion criteria for subject selection
- + Study duration and estimated enrollment period
- + Description of all study-related procedures
- + Outline of the monitoring plan

Statistical considerations

Data management

Procedures to amend the CIP

Deviations from the CIP

Device accountability

Statements of compliance

Informed consent process

Adverse events, adverse device effects, and device deficiencies

Vulnerable population

Suspension or premature termination of the study
Criteria and arrangements for suspension or premature termination of the entire study in one or more investigation sites

Publication policy

Bibliography

Obtaining informed consent

Informed consent should be obtained in writing from the subject and should be documented before any study procedure is performed, except when special circumstances apply, such as subjects requiring emergency treatments.

Sponsors should carefully consider the process and timing for consent, and consent times should be added to the patient's notes to show that no study-related procedures were performed prior to consent.

If new information becomes available that may significantly affect a subject's future health or medical care, that information should be provided in writing to the subjects affected. In most cases, it may be appropriate to ask these subjects to confirm their continued informed consent in writing.

Figure 3. Information needed for the informed consent form:[1]

- Description and purpose of the study
- Potential benefits for the subject
- Risks and inconveniences for the subject
- Alternative treatments or procedures that may be available, and their potential benefits and risks
- Confidentiality statement
- Compensation for study-related injury or adverse event and for participation, if applicable
- Anticipated out-of-pocket expenses
- Points of contact for questions, injury reporting, or emergencies
- Circumstances of study termination or termination of the subject's participation in the study

Note: This list is not intended to be comprehensive; for the full list, please refer to ISO 14155:2011.

Payments, incentives, and conflicts of interest should be included in the informed consent process, as well, even when there is no formal legal requirement to do so.

Ensuring continued quality during study conduct

The application of sound research practices is an ongoing process during study conduct.

Adherence to the CIP

When looking at ongoing study conduct, all subjects recruited must fully meet the inclusion and exclusion criteria defined in the protocol. Any deviations from the eligibility criteria must be documented and reported to IRB/IEC, and possibly regulatory agencies. A well-written CIP helps ensure that these criteria are appropriate and not excessive.

Patient engagement

Patient engagement is especially important in medical device trials, as patients typically have a longer follow-up period when compared to pharmaceutical drug trials. Sponsors should make every effort to make study visits easy and minimize the demand on the patient's time, while still encouraging patients to provide feedback on any safety issues that may arise.

Device handling

Significant care and attention should be paid to device release, packaging, shipment, storage, and accountability. The entire process must be documented and should take into consideration temperature controls and the personnel involved in device handling. If the device is self-administered in the patient's home, there must be procedures regarding how the device will be stored, tracked, and disposed.

Training/re-training

Training is not a one-off event. Teams change, and training must be continuous. Some studies run for months, or even years, and re-training of all staff may be required.

Investigator brochure updates

Device risk assessment in ISO 14155:2011 closely follows ISO 14971 and requires that a summary of the risk analysis, as well as any residual risks, be defined in the investigator brochure (IB). IBs need to be well-written before the start of the study and kept up to date throughout the duration of the study. The sponsor is responsible for updating the IB on an annual basis. If the IB will not be updated, this also must be documented and the results of this review submitted to relevant IEC/IRB or regulatory authorities.

Trial master file/essential document maintenance

The trial master file and essential documents must be readily available for audit and inspection. These documents must be attributable, legible, contemporaneous, original, and accurate. They must also be complete. Key documents require a formal sign-off and version control must be tracked.

Data protection

Documents must be stored in pre-arranged locations and sponsors need to have knowledge of the storage facilities used by vendors. Archiving requirements must be well-defined in vendor contracts. With the increasing use of e-documents, sponsors should have a procedure for validating and archiving these documents and should consider how these documents will be read in the future. Sponsors should keep in mind that safety reporting in device trials is often an area where there may be breaches in data protection, so sites should be trained on the handling of confidential data.

Case report form completion

The case report form (CRF) must be signed once completed by the PI or his or her designee. A sponsor cannot have exclusive control of study data on their servers, so a copy of the CRF must always be kept at the study site.

Accessibility of the PI during monitoring

The PI must support the monitor or auditor and be available to answer questions.

Risk-based monitoring

The level of monitoring can vary, and may be risk-based or even remote, as long as it is well documented and justified. Monitoring plans are required and may include escalation pathways or triggers to increase monitoring. Any copies of source documents must be signed and dated by a member of the site, and a statement is required to certify that the copy is a true representation of the original.

Ongoing assessment of site facilities and equipment

This aspect of study conduct is often overlooked. Ongoing assessment of site facilities and equipment is usually performed by the monitor and must be documented.

Safety reporting

Sponsors are responsible for ongoing safety evaluation and relevant, timely reporting. Safety reporting is essential for identifying device deficiencies, adverse effects, and factors that could affect device operators.

Data management

Electronic systems used in data management require written procedures, verifications, validations, and audits. Staff need to be trained on the use of these systems, as well.

Quality management system

The sponsor is also responsible for having a good quality management system in place, even if they outsource many aspects of the clinical investigation. They are also responsible for verifying the existence of, and adherence to, written procedures at any external organization they may use.

In an environment where increased medical device regulation has better defined the scope of a sponsor's responsibilities in areas such as informed consent, risk assessment, monitoring, and data management, sponsors who adhere to the principles outlined in ISO 14155:2011 are well-positioned to meet the necessary ethical and regulatory requirements.

Planning for successful study close-out

Under ISO 14155:2011, sponsors must also consider processes for site suspension, termination, and closure of the clinical investigation. In case of suspension or early termination, end-of-investigation notifications must be documented and all affected parties must be promptly informed. The sponsor must perform an analysis of the situation and take appropriate corrective actions. If a clinical investigation is to resume, approval or concurrence from the relevant IRB/IEC and, in some cases, the relevant regulatory authority is required.

ISO 14155:2011 provides a comprehensive summary of routine close-out responsibilities and notifications.

After close-out, a study report is required – even if the study was terminated prematurely – and should include:[1]

+ Cover page
+ Table of contents
+ Summary of the investigation, including the purpose and study method used
+ Introduction containing a brief statement placing the study in the context of the development of the device
+ Description of the investigational device and methods, including a summary of the CIP
+ Results
+ Discussion and overall conclusions
+ Ethics
+ Investigators and organization of the study
+ Signature page
+ Annexes and any abbreviated terms and definitions

Archiving and document retention is, in part, per local regulatory requirements in each country where the study is conducted, and ISO 14155:2011 provides a list of the essential documents that should be maintained in sponsor and site files.

Conclusion

ISO 14155:2011 serves as the global standard for good clinical practice in the conduct of device studies. In an environment where increased medical device regulation has better defined the scope of a sponsor's responsibilities in areas such as informed consent, risk assessment, monitoring, and data management, sponsors who adhere to the principles outlined in ISO 14155:2011 are well-positioned to meet the necessary ethical and regulatory requirements. With this higher level of regulatory scrutiny, investing time in getting it right from the beginning and adhering to the quality-by-design principles that are increasingly prevalent in the clinical research industry will lead to a higher likelihood of commercial success.

References

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Nicky Dodsworth is currently Vice President Quality Assurance, Risk & Compliance for Premier Research with responsibility for pharmaceutical and medical device studies.

Nicky is an active member of European Forum for Good Clinical Practice (EFGCP) and, in 2010, she started to run the EMWA Workshop on Quality Awareness in CSR Development. She is also a Senior Associate Member of the Royal Society of Medicine and a Chartered Scientist, an award from the Science Council in the UK bestowed on professional scientists who are practicing and/or advancing science as an integral part of their daily work.

Joanne Emmett | Vice President, Medical Device

With over 20 years of clinical research industry experience, Joanne has a keen focus on operational design and delivery. She began her career in academia within transplant and then cardiovascular research. She joined the CRO space in 1995 and was engaged as a CRA, LCRA, and Project Manager on trials in CNS, Oncology, Respiratory, Cardiovascular Device, and several diagnostic programs. Joanne then moved into oversight and leadership specializing in Clinical and Project Management Delivery, spending time at PRA before joining Premier Research in early 2011.

Since then, Joanne has overseen the operational delivery structures and planning for both clinical and project management. She has focused on the key needs and standards within therapeutic areas and medical device and ensuring core process designations for staffing and oversight.

Joanne chaired the ACRP Poster Committee in 2006 and the Annual ACRP meeting in 2007. She also assisted with development and implementation of the Post Graduate Clinical Research Program at Humber College in Toronto.

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About Premier Research

Premier Research is a leading clinical development service provider that helps highly innovative biotech, medical device, and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional, and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, dermatology, medical devices, neuroscience, oncology, pediatrics, and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.

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