Clinical Investigation Plan and Study Protocol for
Optimization of Prostate Biopsy - Micro-Ultrasound versus MRI (OPTIMUM): A 3-arm randomized controlled trial evaluating the role of 29MHz micro-ultrasound in guiding prostate biopsy in men with clinical suspicion of prostate cancer
(EVU-2021-001)

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Revision History

Date	Author	Rev	Description of Change
28 July 2021	B. Wodlinger	1.0	Initial revision
4 Aug 2021	B. Wodlinger	1.1	Updated per internal feedback for alignment with ISO14155:2020
11 Aug 2021	B. Wodlinger	1.2	Updated per internal feedback
8 May 2023	B. Wodlinger A. Matte	1.2.1	Minor update to remove requirement for individual sites to insert site specific information in the protocol as this information is already included in the CTAs with each site (5.3.3, 5.4.1). New version references location of this information. Wording around study sponsor clarified (1.0, 5.1, 5.3.2) 5.4.6 Clarified patient follow-up survey completed 7-days post biopsy 5.8.1.1 Updated schema figure to correct typo in arm numbers 5.8.3.1 Updated inclusion criterion to clarify prior MRI status (for consistency with blinding in protocol) 5.8.6 Optional Biopsy note taking form added as source document for sites requiring a paper record during biopsy procedure 5.11 Amendment to CIP has been clarified to require only agreement with Study PI not each site PI
19 July 2023	B. Wodlinger A. Matte	1.5	5.9.6 Duplicate entry removed Versions 1.3,1.4 skipped to ensure all sites have later version dates for ethics submission

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1 Purpose

The purpose of this Clinical Investigation Plan and Study Protocol (CIP) is to present information for the *OPTIMUM* clinical investigation, including the scientific basis for the study, the procedural details, the ExactVu High Resolution Micro-Ultrasound System (referred to in this document as *ExactVu*), its safety details, and administrative details.

The CIP was developed by a scientific panel organized by Exact Imaging and led by Dr. Lawrence Klotz who is acting as the overall study principal investigator and sponsor and has been designed in such a way as to optimize the scientific validity and reproducibility of the results of the study in accordance with current clinical knowledge and practice so as to fulfill the objectives of the investigation.

2 Scope

This CIP and the investigation itself are designed to meet applicable requirements and regulations of Health Canada, Europe and US FDA for conducting clinical investigations. The contents of the CIP follow the requirements identified in *ISO 14155 Clinical investigation of medical devices for human subjects*.

The investigation is a non-significant risk (NSR) investigation. ExactVu is cleared for sale in the United States (Class II), Europe (Class IIa), Canada (Class III), and Israel (Class IIa).

This plan is also intended to serve as the Investigator's Brochure for the purposes of this investigation. It also serves as the Study Protocol for the purposes of this investigation and provides the procedure details for the biopsy and pathology analysis.

3 Definitions

Term	Definition
Adverse Device Effect	Adverse event related to the use of an investigational medical device *NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.* *NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.*
Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device *NOTE 1 This definition includes events related to the investigational medical device or the comparator.* *NOTE 2 This definition includes events related to the procedures involved.*

Term	Definition
	NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Case Report Form	Document designed to record all information to be reported to the Sponsor on each subject as required by the CIP
Clinical Investigation Plan and Study Protocol (referred to as "CIP")	A document that states the rationale, objectives, design, medical procedures and proposed analyses, methodology, conduct and record keeping of the clinical investigation. The Clinical Investigation Plan and Study Protocol is designed in such a way as to optimize the scientific validity and reproducibility of the results of the study in accordance with current clinical knowledge and practice so as to fulfill the objectives of the investigation in determining the safety and performance of a device, including undesirable side effects.
Clinical Investigator's Brochure	A compilation of the clinical and nonclinical data on the investigational product which is relevant to the study of the investigational product in human subjects. Its purpose is to provide the investigators and others involved in the investigation with the information to facilitate their understanding of the rationale for, and their compliance with key features of the CIP. The Clinical Investigator's Brochure also provides insight to support the clinical management of the study subjects during the course of the clinical investigation.
Clinically significant cancer	Clinically significant prostate cancer for the purposes of this study is defined as tumors where Gleason score > 6, or ISUP grade > 1. Clinically insignificant cancer is defined as Gleason score = 6 or ISUP = 1.
Comparator	A medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation
Declaration of Helsinki	A statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration of Helsinki was developed by the World Medical Association. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
Device Deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance *NOTE Device deficiencies include malfunctions, use errors, and inadequate labeling.*
ROC curve	Receiver operating characteristic curve, a graphical plot used in statistical analysis is created by plotting the true positive rate (TPR) against the false positive rate (FPR)
Study Monitor	Individual responsible for assessing the investigator's compliance with the CIP and for performing source-data verification. The monitor shall have access to the source documents and other information needed to ensure investigator compliance with the CIP and applicable rules and regulations, and to assess the progress of the clinical investigation.

Term	Definition
	NOTE The monitor is also responsible for reporting on the progress of the clinical investigation, including the compliance of the investigators.
Serious adverse device effect	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Serious adverse event	Adverse event that a) led to death b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury 2) a permanent impairment of a body structure or a body function 3) in-patient or prolonged hospitalization 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function 5) chronic disease c) led to fetal distress, fetal death or a congenital abnormality or birth defect *NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Sponsor	Individual or organization who or which takes responsibility for the initiation and/or implementation of a clinical investigation
TRUS	Transrectal Ultrasound micro-US refers to transrectal ultrasound procedures performed using a high-frequency transducer
Unanticipated serious adverse device effect	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report *NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.*

4 References

1. ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice
2. Council Directive 93/42/EEC (as amended by 07/47/EC) (the "Medical Devices Directive")
3. EU Medical Device Regulations (MDR) 2017/745
4. MDCG 2021-6 Regulation (EU) 2017/745 (April 2021) – Questions & Answers regarding clinical investigation
5. MDCG 2021-08 (May 2021) Clinical investigation application/notification documents
6. MDCG 2021-20 (July 2021) Instructions for generating CIV-ID for MDR Clinical Investigations

7. EN ISO 13485:2016 Medical Devices - Quality Management Systems – Requirements for regulatory purposes
8. 21 CFR Part 812 Subpart B – Investigational Device Exemptions
9. Guidance for Industry and FDA Staff - Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers
10. ISO 14971:2019 Medical devices – Application of risk management to medical devices
11. Clinical Trials.gov, U.S. National Library of Medicine
12. Canadian Medical Device Regulations, Good and Drug Act, SOR/98-282
13. Health Canada Guidance Document, Applications for Medical Device Investigational Testing Authorizations Effective Date 208/10/01

5 Clinical Investigation Infrastructure

5.1 Responsibilities

All parties involved in the conduct of the clinical investigation shall share the responsibility for its ethical conduct in accordance with their respective roles in the clinical investigation.

The investigation will be conducted by a consortium of investigators from 12-20 international institutions in Canada, the United States, and Europe.

Exact Imaging, as well as the study principal investigator/study sponsor (Dr. Laurence Klotz), and each site principal investigator shall agree to the CIP and any amendments and indicate their approval and agreement by signing and dating the signature page of this CIP.

5.2 Contents of the CIP

The CIP includes the information about the topics identified in the following sections. If the required information is written in other documentation related to the investigation, for example consent forms or case report forms, such documentation shall be referenced in this CIP, and controlled according to Exact Imaging's standard operating procedures.

Applicable documents shall be included with this CIP in regulatory submissions as required, and any other referenced documents shall be made available on request to each institution or its reviewing research ethics board (IRB/REB).

5.3 General information

5.3.1 Identification of the CIP

The title for the clinical investigation is *Optimization of Prostate Biopsy - Micro-Ultrasound versus MRI (OPTIMUM): A 3-arm randomized controlled trial evaluating the role of 29MHz micro-ultrasound in guiding prostate biopsy in men with clinical suspicion of prostate cancer*.

The revision number and date of the document are indicated in the Revision History. The Exact Imaging identifier for the investigation is *EVU-2021-001*.

5.3.2 Identification of the sponsor

This is an investigator-initiated trial, which is organized by a consortium of Principal Investigators led by the lead study site investigator and study sponsor:

Dr. Laurence H. Klotz
Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto
2075 Bayview Ave. #MG408, Toronto, ON
M4N 3M5
Canada

Laurence.klotz@sunnybrook.ca
Phone: 416-480-4673
Fax: 416-480-6121

Exact Imaging Inc. is the manufacturer of the ExactVu Micro-Ultrasound system used in this study and has agreed to provide organizational and limited support for this study:

Exact Imaging Inc.
7676 Woodbine Avenue, Unit 15
Markham, ON
L3R 2N2
Canada

Primary contact
Brian Wodlinger
VP, Engineering & Clinical
bwodlinger@exactimaging.com
Cell: (647) 527-9032
Office: 905-415-0030 ext. 204
Toll-free: 1-855-233-1919 ext. 204

Secondary contact
Andrea Matte
Clinical Trial Monitor
amatte@exactimaging.com
Cell: (416) 602-5012

5.3.3 Identification of the investigators

Investigators are identified on the site's ethics's approved informed consent form. In addition, the study sites and investigators are listed on the ClinicalTrials.gov website. The website is updated at least once yearly. Address of the study site institution may be found in the signed clinical trial agreement (CTA).

5.3.4 Overview of the investigational protocol

The investigational protocol describes a study designed to compare the ability of ultra-high resolution transrectal micro-ultrasound (microUS) and multiparametric MRI (mpMRI)/US fusion to guide prostate biopsy.

Micro-ultrasound is a novel imaging modality that provides a dramatic improvement in ability to visualize abnormalities of the prostate compared to conventional ultrasound imaging. This improvement in visualization has wide reaching consequences for clinical protocols from screening, through detection, and into treatment and treatment monitoring. However, no randomized controlled evidence is available to compare the efficacy of microUS-guided prostate biopsy with the gold standard mpMRI/US fusion biopsy procedure. This investigational protocol aims to provide such evidence.

The ExactVu device in particular, and micro-US in general have been studied in a number of other investigations, including a pilot study performed at Johns Hopkins University School of Medicine, in which differences between Ultra High Resolution (UHR) using ExactVu's predecessor (ImagistxProstate) and Low Resolution (LR) transrectal ultrasound in their ability to detect cancerous foci in 25 patients were compared, along with safety and efficacy of this technology.[1] Three other previous studies have been approved through Western IRB, including protocol 20131849 which provided the first randomized clinical trial on micro-US, Western IRB protocol 20162036 which provided a small initial case series comparison of mpMRI and micro-ultrasound in the active surveillance population, and Western IRB protocol 20181898 compared micro-ultrasound targeted biopsy to MRI targeted biopsy within the same patients. Results from all 3 studies were positive and 2 have recently been presented.[2,3] Results from the 3rd as yet unpublished study are available on clinicaltrials.gov.

Details about objectives of the investigation are described provided in section 5.7.1. The investigational protocol was developed by a consortium of experts in prostate cancer early detection, and will be followed by the investigative team. The Study Principal Investigator/Sponsor is responsible for the contents of the investigational protocol, and for monitoring the investigation.

5.4 Device Description

The ExactVu device is a new ultra-high resolution ultrasound system. It uses a specialized high-frequency transducer, developed by Exact Imaging Inc, to be used by qualified urologists, radiologists, and trained clinicians for real-time prostate imaging and biopsy procedures. It also supports a customized low-frequency transducer. The platform on which ExactVu operates represents the state of the art in high-resolution micro-ultrasound technology. The ExactVu system first received pre-market clearance from the FDA on December 2nd 2016, and most recently on May 12th 2019 for the following indications for use (similar in Canada and Europe): *The ExactVu High Resolution Micro-Ultrasound System is intended for use by qualified physicians, physician assistants, sonographers, and ultrasound technicians in a healthcare facility for diagnostic ultrasound imaging or fluid flow analysis of the human body in B-Mode (2D), Color Flow Imaging Modes (Color Doppler and Power Doppler) and Combined (B-Mode + CFI Modes).*

The indications for use are:

- *Small Organ*
- *Transrectal*
- *Abdominal The system may be used with patients of all ages, but is not designed for pediatric or fetal use. The system is contraindicated for direct cardiac application and for ophthalmic use or any application that causes the acoustic beam to pass through the eye.*

The ExactVu device is also cleared for sale as a Class 3 device in Canada (Device Licence # 98667 – ExactVu High Resolution Mico-Ultrasound System) and has received CE mark for Europe (CE 2797) , both with the indication for diagnostic ultrasound imaging and prostate biopsy.
For the purposes of this clinical investigation, the ExactVu device is being compared to a conventional-ultrasound-based mpMRI Fusion platform. Like the ExactVu, this comparative Fusion platform has received pre-market clearance from the FDA, Health Canada, and CE mark.

5.4.1 Device Identification

Information for the Conventional Fusion Systems and transducers is located in Exhibit C of the Clinical Trial Agreement

5.4.2 Purpose of the device in the context of the investigation

For this investigation, both ExactVu and the conventional Fusion system will be used to perform the following tasks, consistent with their indications:

- Transrectal imaging of the prostate where clinically indicated (for example, for volume measurement or prior to biopsy)

5.4.3 Materials that contact the patient

The components of devices that will be in contact with tissues or body fluids include the sterile biopsy needle guide.

During use, the transducers will be covered in a conductive coupling gel and covered by a sterile transducer sheath, and therefore will not be in direct contact with the patient. If the sheath were to be compromised during the procedure, then the transducer, biopsy needle guide and biopsy needle could contact tissues or body fluids.

5.4.3.1 EV29L Transducer construction materials

The materials used in the construction of the ExactVu transducer are:

- Rexolite by C-LEC Plastics – a polystyrene microwave plastic used for the transducer lens
- Epotek 301 – an epoxy used for gluing the housing sides together, and for gluing the lens to the housing
- PEEK LSG provided by Quadrant – a life sciences grade plastic used to construct the housing

Each material has been tested on its own to meet applicable criteria of ISO 10993-1 – Biological evaluation of medical devices.

The transducer may contact tissues or body fluids only if the sterile transducer sheath is compromised.

5.4.3.2 Biopsy needle guide construction materials

The biopsy needle guide for use with EV29L is manufactured for Exact Imaging by CIVCO. CIVCO is responsible for the selection of materials for this needle guide and for ensuring that the guide complies with the applicable criteria of ISO 10993 – Biological evaluation of medical devices.

CIVCO is also responsible for completing sterilization and packaging validation.

5.4.3.3 Qualified Gels

This investigation recognizes Health Canada and FDA's recommendations for the use of sterile gels for invasive procedures that pass a device through tissue (i.e., in biopsy procedures).
Where non-sterile ultrasound gel is used, investigators must take steps to ensure that the product being used is not contaminated, and the container must be sealed appropriately when not in use. Gels whose packaging indicates that they are to be used for external procedures only must not be used. Where non-sterile ultrasound gel is used, the use of single-dose gels is recommended.

5.4.3.4 Sterile transducer sheath

Sterile transducer sheaths will be used for imaging procedures. For biopsy procedures using the EV29L transducer, off-the-shelf sterile transducer sheaths will be supplied by Exact Imaging.

5.4.3.5 Transducer reprocessing

Investigators will be provided with instructions for cleaning the ExactVu system and the high-level disinfection of applicable components. These instructions meet the applicable criteria of FDA guidance documents regarding diagnostic ultrasound marketing/licensing.

The instructions can be found in the document:

- Care, Cleaning and Use Guide for EV29L™ High Resolution Transrectal Side-fire Transducer

Reprocessing of the competitive conventional Fusion system should be performed per manufacturer's recommendations.

5.4.4 Instructions for use

Instructions for use for ExactVu and its accessories are provided in ExactVu labeling.

Information describing the workflow for this this clinical investigation can be found in this CIP, which will be provided to investigators.

5.4.5 Training requirements

ExactVu is intended for use by qualified physicians and radiologists. Its use does not require any additional training in medical procedures or principles of ultrasound technology.

The investigators and applicable personnel that will participate in this clinical trial are familiar with the procedures that comprise this protocol, as they have already successfully completed training on the ExactVu platform and have used the high-frequency micro-ultrasound to visualize the prostate and guide prostate biopsy in clinical practice for more than 25 cases and have been certified as competent through Exact Imaging's Mastery Program to at least Level 3 "Advanced User".

New training for the purposes of this protocol involves:

- An overview of the case report form, and the case data to be recorded

This training will be documented on the training records that are controlled as per Exact Imaging standard operating procedures.

Each investigator must complete this training before using ExactVu to perform biopsy procedures for this study.

5.4.6 Medical procedures

Medical procedures to be performed in the study consist of subject preparation and imaging. The procedure will be the same for all subjects.

The detailed procedure is as follows:

1. Screening and consent visit (may be combined with visits 2 and/or 3):
    a. Patient meets inclusion criteria
    b. Patient willing to be randomized
    c. Informed consent and randomization
2. Prior to biopsy ***(MRI/US and MRI/MicroUS arms only):***
    a. Radiologist reads and annotates mpMRI for use during Fusion biopsy
    b. Annotated mpMRI is provided
        i. ***MRI/MicroUS arm:*** MRI is not shared with operator until unblinding
3. Biopsy visit:
    a. Save sweep of prostate
    b. ***(MicroUS and MRI/MicroUS Arms)*** Record suspicious regions (PRI-MUS 3+)
    c. Standard of care biopsy
        i. Including targeted and systematic samples
        ii. Targeted samples must be potted and labeled separately per best practices
    d. Standard post-biopsy follow-up

The subject is not required to come for additional clinic visits in the context of the study.

Further healthcare decisions and follow-up are outside the scope of this study. The subject's participation in the study is completed 7 days following the biopsy session when they will be asked to answer a short questionnaire on their experience.

5.5 Justification for the Design

Conventional-ultrasound has demonstrated poor sensitivity for detection of prostate cancer, and this has translated to a standard systematic biopsy strategy which unfortunately still has an unacceptable 30% false negative rate. Multi-parametric MRI has entered clinical use as a superior technique to conventional ultrasound, but still carries a 14% false negative rate[4] and is significantly more expensive, requiring a second specialty to be involved in the care path. While the technique is more sensitive it is not clear whether there is a strong enough relationship between the MRI abnormalities and the cancerous foci to merit its use for treatment planning, follow-up, and screening. Improvements in prostate cancer imaging are needed.

MicroUS uses high frequencies (29 MHz) to improve resolution of prostate ultrasound images, and provides a protocol for assessing risk in these images known as **PRI-MUS**™ (**P**rostate **R**isk **I**dentification using **M**icro-**U**ltra**s**ound)[5]. Using this technology, the predecessor of ExactVu was recently demonstrated by a team at Johns Hopkins Medical to have improved ability to image cancerous foci over conventional-ultrasound, and to have potential improved efficacy in identifying higher grade tumors[1]. More recent studies have extended these findings, by providing further evidence of the superiority of micro-US to conventional-ultrasound[2] and preliminary evidence that micro-US may provide similar improvements to mpMRI.[3,6–8]

While single center and non-randomized studies support the hypothesis that micro-ultrasound provides similar biopsy quality to mpMRI, a higher level of evidence is required to change widespread clinical practice. This study will provide the highest level of randomized controlled evidence to support the non-inferiority of microUS for biopsy guidance and additionally allow

estimation of the synergy between microUS and mpMRI to determine whether a combined approach is useful.

5.5.1 Evaluation of pre-clinical data

Exact Imaging has not performed pre-clinical testing using animals using the current version of ExactVu. Tests using animals were performed prior to the pilot study described in section 5.5.2.1, using previous generations of the technology used in ExactVu, however these studies were not conducted by Exact Imaging.

5.5.2 Clinical evaluation

5.5.2.1 Previous clinical experience: Johns Hopkins Pilot Study

Johns Hopkins Urology conducted a small-scale clinical trial in 2011/2012 using the *previous generation* of the technology used to design and manufacture ExactVu. This trial was conducted to compare the differences between Ultra High Resolution (UHR) and Low Resolution (LR) transrectal ultrasound in their ability to detect cancerous foci in 20 patients.

Patients were imaged pre-operatively with both micro-US and LR-TRUS. Areas of altered echogenicity ≥ 5mm on sagittal views were identified by a radiologist with an expertise in ultrasound blinded to pathology results. Actual areas of prostate cancer ≥5mm identified at sagittally-sectioned RP specimen were correlated to abnormal foci on both imaging modalities. Sensitivity and specificity analysis were performed for each imaging modality. A total of 56 cancerous foci were pathologically identified. micro-US was superior to LR-TRUS in the identification of these foci ($p = 0.01$).

The results of this pilot trial showed clinically meaningful increases in Sensitivity (56.5%), Specificity (21.1%) and PPV (predictive positive value) (42.0%) with ExactVu versus conventional low resolution ultrasound.

Results of the study were published in *Urologic Oncology*[1]. This protocol follows a similar design except using the current ExactVu instrument and with the addition of the PRI-MUS risk scale for consistent and repeatable analysis of the images. Further, this protocol includes improved registration techniques to align pathology and imaging, new secondary outcomes, and neglects the conventional ultrasound comparator in favor of the improved pre-operative mpMRI.

5.5.2.2 Previous clinical experience: Multi-Center trial of high-resolution transrectal ultrasound versus standard low-resolution transrectal ultrasound for the identification of clinically significant prostate cancer (2013-UHR-002)

Exact Imaging recently conducted a large scale clinical trial (beginning in 2013, 2000 patients, under WIRB Protocol 20131849) to demonstrate that micro-US is superior to conventional LR-TRUS in guiding prostate biopsies (systematic and targeted) among men without known prostate cancer and with an indication for prostate biopsy.

Results from this trial have been analyzed and support the value of micro-US and the PRI-MUS protcol[2]. Number and grade of adverse events between the micro-US and conventional ultrasound arms of the trial were identical (3 each). 2 of the three events in the micro-US arm were cases of post-biopsy bacteremia, suggesting a rate of 0.4% which is well within published rates for this procedure. The third adverse event in the ExactVu arm was a patient who presented at the emergency room complaining of fever. No fever was detected on admission, no elevation

in white blood cell count or growth in culture was found. The patient was discharged the following day with a prolonged course of antibiotics despite the lack of evidence of infection. All adverse events were anticipated events.

5.5.2.3 Previous clinical experience: Urology of Virginia Case Series (UHR-2016-001)

A small 9-subject case series was performed under WIRB protocol 20162036 to provide guidance to clinical users on the appearance of mpMRI lesions visualized with micro-ultrasound. Results from this study were first presented at the EAU 2018 meeting and have recently been accepted for publication in the Canadian Urological Association Journal.[3,9]

This small series demonstrated superior sensitivity by micro-US (89% vs 56% for mpMRI), particularly against relatively inexperienced mpMRI reviewers and for small Gleason Sum 7 lesions. Both micro-US and mpMRI provided superior targeting sensitivity compared to conventional ultrasound (p=0.02). mpMRI lesions were retrospectively visible under micro-US, making it easier to perform accurate targeted biopsy.

5.5.2.4 Previous clinical experience: Reports in the literature from cohort studies

Cohort studies are available from two European centers demonstrating promising detection rates and sensitivity relative to mpMRI. Astobieta et al.[6] reported on 41 consecutive subjects biopsied using the ExactVu micro-ultrasound system with available mpMRI studies for comparison and targeted biopsy. mpMRI correctly predicted 28/41 subjects with clinically significant prostate cancer (68% sensitivity) while micro-ultrasound predicted 40/41 (98% sensitivity). This improvement in sensitivity was significant with p<0.001.

Similarly, Lughezzani et al[10] reported on their first 60 subjects with both mpMRI targets and micro-ultrasound guided biopsy as part of their prospectively maintained prostate biopsy database. In this dataset, in which all subjects had positive mpMRI, sensitivity and negative predictive value of micro-ultrasound were 83% and 80% respectively, while the sensitivity of mpMRI was similar at 85%. This cohort was later updated to 320 subjects with equal detection rates of csPCa between mpMRI and MicroUS biopsy strategies (116/320 each).[11] Wiemer et al[12] performed a similar study on 159 subjects undergoing biopsy with both mpMRI and microUS targets and found a 95% relative sensitivity for microUS targeted biopsy with significant added value on top of systematic and mpMRI targeted samples.

5.5.2.5 Previous clinical experience: Registry studies

Klotz et al.[13] published the experience of 1,040 biopsy procedures at 11 institutions. In total 39.5% of subjects were diagnosed with csPCa and both mpMRI and microUS were extremely sensitive to predict which would eventually be diagnosed (90% vs. 94%, microUS superior with p=0.03). Specificity and PPV were similar between the two modalities though NPV was higher for microUS (85% vs. 77%). The principal limitations here were the lack of randomization and lack of blinding at some centers due to the registry design.

5.5.2.6 Literature review

A critical literature review was performed to establish the relative detection rates of prostate biopsy in the literature. The conclusions for the evaluation are presented in section 5.20. (Note that bibliographic references specific to the literature review are also presented in section 5.20.)

5.6 Risks and Benefits

This clinical investigation will ensure that

- the residual risks, as identified in the latest revision of the risk and hazard analysis of the ExactVu system and
- risk(s) to the subject associated with the clinical procedure including follow-up procedures required by the CIP

will be balanced against the anticipated benefits to the subjects.

The sponsors will ensure that risk management shall be carried out and evaluated throughout the clinical investigation.

5.6.1 Device risk analysis and management

The Risk Management Plan for ExactVu and the related hazard analysis was conducted in accordance with the latest revision of ISO 14971 and with reference to Exact Imaging's quality system procedures. All anticipated adverse device effects are captured in the latest revision of the Risk and Hazards Analysis document of the ExactVu system.

5.6.2 Risks associated with participation in the clinical investigation

There are no known risks in the use of ultrasound as it will be used in this investigation. There may be slight discomfort caused by the ultrasound probe inserted in a subject's rectum, as in a standard imaging or biopsy procedure. The biopsy procedure itself carries certain risks, including sepsis, however these are beyond the scope of this investigation since the particular device used for imaging during the biopsy has no effect on these risks.

5.6.3 Risks associated with the investigational device and its related clinical procedure

Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design and conduct of a clinical investigation. The risk assessment shall include or refer to an objective review of published and available unpublished medical and scientific literature as outlined in Section 5.5.2.6. Note that the ExactVu device is cleared for sale in Canada, the United States, and has received CE mark for Europe, with the indication for diagnostic ultrasound imaging and prostate biopsy.
When used in accordance with their Indications and Instructions for Use, the Risk-to-Benefit and Safety of the ExactVu System are deemed acceptable based on review of state-of-the-art literature covering the subject and equivalent device.

As ExactVu System is used solely to image, the probable health benefit of the additional information provided outweighs the risk associated with its use. Thus, as the risks associated with the intended use of ExactVu System constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, and conforms to MDD Essential Requirement 1, and MDR GSPR 8..

Similarly, all anticipated adverse device effects shall be disclosed in the informed consent form.

5.6.4 Possible interactions with concomitant medical treatments

No new interactions with concomitant medical treatments are anticipated related to the use of ExactVu. ExactVu is already intended and cleared by FDA to perform the prostate imaging procedure clinically. ExactVu is designed to introduce no increased risk when compared to conventional ultrasound.

5.6.5 Risks associated with the Clinical investigation process

Risk management will be applied to both the planning and the conduct of clinical investigations, in order to ensure the reliability of the clinical data generated and the safety of subjects.

The sponsor shall identify, assess and control risks associated with clinical investigation processes to ensure the ethical and scientific conduct of the clinical investigation and the credibility of the clinical investigation results.

Clinical risks related to the clinical procedures, including follow-up procedures required by the CIP other than those related to the medical device, shall be identified from the literature review and their disclosure in the CIP and if applicable, the informed consent, shall be determined by the sponsor and managed in the interest of subject safety.

The sponsor will also consider applicability of Risk control measures at the clinical quality management system level, clinical investigation planning and conduct level (e.g., clinical investigation design, data collection, informed consent process)

5.6.6 Steps that will be taken to control or mitigate the risks

The latest revision of the Risk and Hazards Analysis document of the ExactVu system will outline the necessary design control and other mitigations taken to mitigate or lessen the risk probability number of the hazards identified.

In addition, the latest revision of the Risk and Hazards Analysis document of the ExactVu system will also outline a rationale for the benefit-risk ratio.

5.7 Objectives and Hypothesis

5.7.1 Objectives

Primary Outcome: Difference in detection rate of Grade Group > 1 Prostate cancers (csPCa) found using MicroUS + systematic biopsy and using mpMRI/US Fusion + systematic biopsy.

Secondary (powered) Outcome: Difference in detection rate of Grade Group > 1 Prostate cancers (csPCa) found using MicroUS + mpMRI + systematic biopsy vs. mpMRI/US Fusion + systematic biopsy.

Secondary (unpowered) Outcomes:

- Difference in negative predictive value of highest risk score per patient (PI-RADS or PRI-MUS) for prediction of csPCa on biopsy
- Added value of each biopsy technique

- Added value of systematic biopsy over targeted biopsy
- Difference in health economic variables:
    - Procedure time
    - Cost (including MRI scan / MRI Magnet time)
    - Radiologist time
- Patient Satisfaction
    - Subpopulation analysis of men in the MicroUS-only arm with prior MRI vs those without

5.7.2 Hypothesis

Primary Hypothesis: The micro-ultrasound biopsy procedure is non-inferior to the mpMRI/US fusion biopsy procedure with a threshold of 10% and thus reduce the need for MRI prior to biopsy.

5.7.3 Claims

There are no claims related to the intended performance of the system that are to be verified in the analysis related to this investigation, aside from those related to the objectives.

5.7.4 Risks

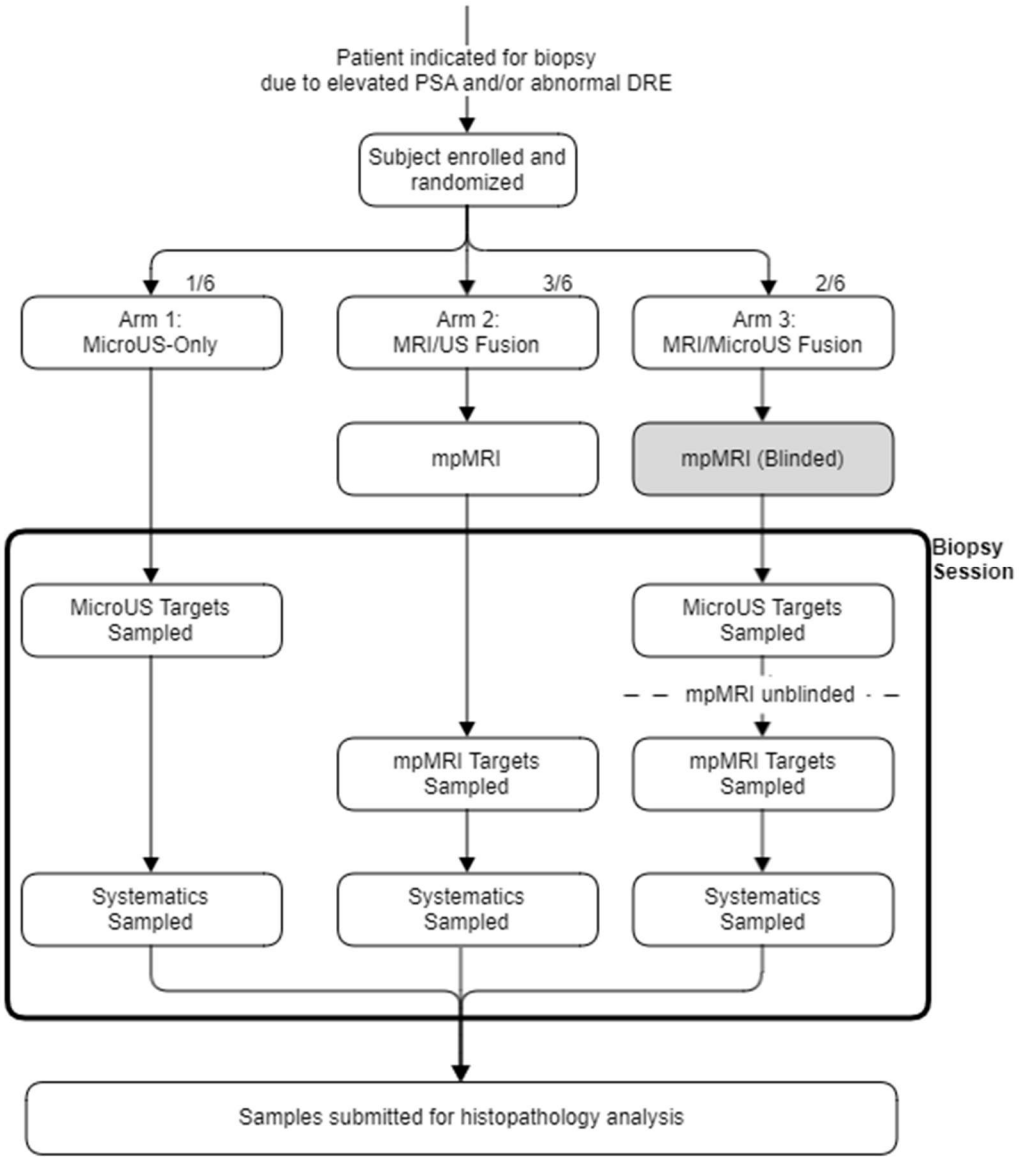
There are no risks or foreseeable adverse device effects that are to be assessed in the investigation.

5.8 Design of the Clinical Investigation

5.8.1 General

5.8.1.1 Type of clinical investigation

The investigation is a randomized controlled study where all subjects have an indication for prostate biopsy. A 3-arm randomization with unequal weighting will be used to compare three biopsy strategies: MicroUS only, n, MRI/US fusion, MRI/MicroUS ("FusionVu") fusion. The overall study schema is presented below.



5.8.1.2 Avoiding bias

The imaging scans will be saved for later analysis. To avoid bias from a single operator performing the scan, multiple readers may be asked to comment on the image quality.

5.8.1.3 Endpoints

Primary endpoint
Number of men diagnosed with csPCa based on the pathology samples collected during the biopsy procedure through:

- MicroUS samples (targeted and systematic samples taken under microUS imaging only without mpMRI)
- mpMRI/US Fusion samples (targeted and systematic samples taken under conventional ultrasound imaging with mpMRI targets)

Secondary endpoints
As above, with the addition of combined results for men undergoing Fusion biopsy on the microUS system:

- mpMRI/MicroUS samples (targeted and systematic samples taken under microUS imaging with mpMRI)

5.8.1.4 Variables

The primary analysis will be performed at subject level.

5.8.1.5 Assessing variables

The analysis to be performed on data collected during the investigation will be done using a generally accepted statistical software package such as MATLAB, R, SPSS, or SAAS. The software will not be 'calibrated' other than if there are instances where the software does not perform as required against unusual or exceptional data.

5.8.1.6 Replacing subjects

Case data for all enrolled study subjects will be included in the analyses. Because a subject's involvement ends following biopsy, and because it is not expected that a subject will drop-out after this procedure, the need to replace subjects is expected to be unlikely.

If a subject needs to be replaced, they will be consented as per processes described for all study subjects.

5.8.2 Medical devices and comparators

See section 5.4.

5.8.3 Subjects

5.8.3.1 Inclusion criteria for subject selection

Subjects will be recruited to participate in the investigation as follows:

1. Men indicated for prostate biopsy due to elevated PSA and/or abnormal DRE

2. No history of prior prostate biopsy
3. No history of genitourinary cancer, including prostate cancer
4. ≥18 years of age
5. No contraindications to biopsy
6. No contraindications to mpMRI
7. No history of mpMRI for clinical investigation of prostate cancer within 12 months prior to screening and enrollment in the study

5.8.3.2 Exclusion criteria for subject selection

Subjects will be excluded from being included in the investigation if any of the following is true:

1. History of prior prostate biopsy
2. History of genitourinary cancer, including prostate cancer
3. Contraindications to biopsy
4. Contraindications to mpMRI

5.8.3.3 Criteria and procedures for subject withdrawal or discontinuation

Subjects may withdraw from the investigation at any time with no effect on their future care.

If a subject wishes to stop participating in the investigation, they are to do so by notifying the Principal Investigator by phone or letter.

If a subject withdraws from the investigation prior to having his biopsy procedure performed, the procedure will be performed as per the normal standard of care. There will be no further follow-up with this subject in the context of this investigation.

Data considerations for this case are provided in section 5.9.

5.8.3.4 Point of enrolment

Men meeting the criteria defined in section 5.8.3.1 will be asked to participate in the study and will be presented with a *Research Subject Information and Consent Form.*

Subjects are considered to be enrolled in the investigation when they return a signed Research Subject Information and Consent Form to the Principal Investigator.

When a signed form is presented, the subject agrees to join the investigation, and accepts the provisions on the form, including an understanding that he may leave the investigation at any time.

5.8.3.5 Total expected duration of the clinical investigation

The investigation is expected to take approximately 2 years maximum.

5.8.3.6 Expected duration of each subject's participation

The procedure follows the standard of care, in that it is performed immediately before a clinically indicated transrectal imaging procedure. Subjects are not required to come for additional clinic visits in the context of the investigation.

Participating in the trial will add approximately 2 minutes to the subject’s procedure time.

5.8.3.7 Number of subjects

The number of subjects to be included in the trial is 1200 across all participating sites. ESites will be allocated between 30-200subjects.

5.8.3.8 Estimated time needed to select this number (i.e. enrolment period)

The investigation is expected to take approximately 2 years total. This is intended to provide adequate time to enroll and study the projected number of subjects in the trial. A subject's participation in the investigation is completed following the follow up survey 7 days post biopsy.

5.8.4 Procedures

5.8.4.1 Clinical investigation-related procedures

The procedures affecting subjects and investigators participating in the investigation are:

- Consent / Subject Enrolment as described in section 5.15
- Training as described in section 5.4.5
- Medical procedure as described in section 5.4.6
- Record Data on Case Report Forms as described in section 5.8.6
- Analyze Data as described in section 5.9

5.8.4.2 Sponsor activities

This is an investigator-initiated study, and the international group of Principal Investigators are responsible for this clinical investigation including the preparation of this CIP. These responsibilities are presented in detail, to facilitate planning of this investigation.

Exact Imaging will provide assistance in accordance with an approved budget that is incorporated into the Clinical Trial Agreement.

Further detailed sponsor responsibilities can be found in Appendix A.

5.8.4.3 Compromising factors

There are no known foreseeable subject-related factors such as subject baseline characteristics and lifestyle that may compromise outcomes or the interpretation of results.

5.8.4.4 Follow-up period

Following a subject's procedure, there is no further physical follow-up involved in the context of this investigation.

5.8.4.5 Post-investigation care

No further medical care is provided within the context of this investigation.

5.8.5 Monitoring Plan

A risk-based monitoring plan shall be developed by the sponsor which will be tailored according to the stage of clinical development and the type of clinical investigation.
The sponsor shall ensure, through oversight of the clinical investigation and timely adverse event

reporting, that unanticipated adverse device effects are identified and investigated rapidly so that, where necessary, additional risk control measures can be implemented. With the outcome of the risk assessment, a monitoring plan shall be developed outlining:

a) the risks associated with the clinical investigation and adequate information on relevant risk control measures;
b) the processes that need to be monitored including data that is required to be verified in source documents;
c) the monitoring methods (on-site, a combination of on-site and where justified, centralized monitoring, as appropriate);
d) the responsibilities;
e) the procedures and requirements for the investigation's oversight;
f) the methods for documenting and communicating monitoring results;
g) the methods for obtaining compliance;
h) the process for escalation in case of continuous or egregious non-compliance;
i) those aspects of the clinical investigation which need special attention because if performed incorrectly or inadequately, would compromise the protection of human subjects or the integrity of the data;
j) special requirements regarding personal data protection.

The Study Monitor role for the clinical investigation will be provided by the sponsor. The sponsor will determine the extent and nature of monitoring for the clinical investigation that will be based on continuing risk assessment. The Study Monitor will adhere to the monitoring responsibilities, which include verifying that:

a) compliance with the CIP is maintained and any deviation from the CIP is discussed with the clinical investigators, documented and reported to the group of Principal Investigators,
b) the device is being used according to the CIP, and if modifications are required either to the device or its method of use or to the CIP, this need is reported to the group of Principal Investigators,
c) the clinical investigators have and continues to have staff and facilities to conduct the clinical investigation safely and effectively,
d) the clinical investigators have and continues to have access to an adequate number of subjects and devices,
e) signed and dated informed consent forms have been obtained from each subject at the time of enrolment and before any study-related procedures are undertaken,
f) the data in the case report forms are complete, are recorded in a timely manner and are consistent with the source data, the procedures for recording and reporting adverse events and adverse device effects to the sponsor are followed,
g) there is a process in place for device accountability and traceability and that it is maintained,
h) maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is performed and documented,
i) subject withdrawal and/or non-compliance is documented and discussed with the clinical investigator and reported to the group of Principal Investigators,
j) findings of non-compliance or required modifications shall be reviewed with the investigator and disclosed in a written monitoring report to the group of Principal Investigators.

Source data will be recorded on case report forms (CRFs) as described in section 5.8.6.

5.8.5.1 Site Visits

Further to Exact Imaging's role for the investigation, Exact Imaging will provide support to ensure the quality of data related to the investigation by:

- on-site visits to each site at the beginning and end of the study, and as required to ensure optimal image quality and assist with protocol training
- thorough review of CRF data to identify and follow-up on missing data, inconsistent data, data outliers, and potential CIP deviations that may be indicative of systemic or significant errors in data collection and reporting and as determined by the study sponsor

An on-site visit at the beginning of the investigation will include the following activities:

1. Review of supplies required for the investigation
    a. Check that there continues to be an adequate supply of sterile transducer sheaths and needle guides

2. Review of device maintenance and image quality assessment to ensure devices are functioning correctly

3. Review issues with investigators
    a. Discuss and investigate any performance issues and device deficiencies and resolved as required. These issues will be documented according to Exact Imaging service procedures including details about steps taken to resolve issues
    b. Review any changes to the investigative team and update details in the CIP as required
    c. Provide training where changes to the investigative team requires it

Any on-site visits during the investigation will include the following activities:

1. Review subject enrolment

2. Review study data
    a. Review data collected on CRF
    b. Check CRF for completeness and accuracy. Ensure CRFs are filled out properly
    c. Check ExactVu for images. There must be at least one image saved on the system to correspond to each subject.
    d. Verify data. Compare images stored on ultrasound system with CRF data and pathology report

3. Copy and collect image data

4. Copy and collect completed CRFs

Along with providing assurance of the quality of investigational data, these actions will allow Exact Imaging to assess compliance with the CIP and required procedures. Exact Imaging staff will make all documentation and reports from these visits available to the site Study Monitor for inclusion in study records as required.

For cases in which Exact Imaging personnel observe biopsy procedures during a site visit, they shall neither perform medical procedures nor contact the study subject, but will provide support through instruction where required.

5.8.6 Case Report Forms

The case report form(CRF) to be used in this investigation is designed to collect information about the subject medical history and the necessary primary endpoints for the primary analysis. Paper CRF may be used to record data however; if they are used they will be considered source data.

Source data will be recorded as follows:
- Subject demographics (de-identified)
- Genitourinary surgical/medical history
- Biopsy note taking form (optional paper form for taking notes during biopsy procedure)
- Survey questions to be completed following biopsy

Along with the data accuracy checks listed above, Exact Imaging will also check data prior to and during analysis as follows:
- Logic checks on data, and follow-up on unusual data.

Analysis of data is described in the subsections of section 5.9.

The case report form to be used in this investigation was drafted collaboratively with the group of Principal Investigators and is controlled as per Exact Imaging's standard operating procedures.

5.8.7 Identity of study subjects

At all times throughout the clinical investigation confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in the reports and any publication of the clinical investigation data.

It is the responsibility of the Study Coordinator under supervision of the Principal Investigator(PI) to maintain the privacy of the subject throughout the investigation. The Study Coordinator or PI will make a subject's personal information available to the appropriate parties, should it be required for monitoring, auditing or inspection by the Ethics Board/IRB if applicable.

It is the responsibility of the study site to de-identify subjects, and provide the resulting subject identifier to those involved with the analysis of the case data. This subject identifier will be recorded on CRFs, on ExactVu, and on pathology records. Lists of subjects' names and identifying information will be maintained separately from case report forms, and will be accessible to the Study Coordinator (or designate).

Similar de-identification will be applied to any DICOM imaging files that may exist for a subject and that may be used by to analyze case data.

Centre	De-identification scheme
Centres are listed using 2 or 3 unique letters	On CRFs and on the ultrasound system(s) subjects will be identified alphanumerically and sequentially, using Site Centre-01, Site Centre-02, etc.

5.9 Statistical considerations

5.9.1 Statistical design, method and analytical procedures

Case data will be analyzed using Excel and MATLAB or other standard statistical software package.

Overall number of subjects diagnosed with csPCa in the MRI/US arm will be compared to number of subjects diagnosed with csPCa using microUS targeted and systematic biopsy samples in the MicroUS and MRI/MicroUS arms (i.e. discounting the MRI targeted samples taken after blinding in the MRI/MicroUS arm). A non-inferiority threshold of 10% will be used. Assuming a csPCa detection rate of 43% in each group, 1082 subjects are needed for 90% power.

For the secondary fusion comparison overall number of patients diagnosed with csPCa will be compared between MRI/US Arm and MRI/MicroUS Arm with a non-inferiority threshold of 10%. Assuming a csPCa detection rate of 42% in the MRI/US Arm and 44% in the MRI/MicroUS Arm 358 subjects per group is required for 90% power.

Details of the design are presented in section 5.8.1.

5.9.2 Sample size

The trial will include 1200 subjects as per the table below.

Endpoints	MRI/US Arm	MicroUS Arm	MRI/MicroUS Arm
Primary – MRI vs. MicroUS	541	541	
Secondary – Fusion Comparison	358	-	358
Minimum Sample Size (N=1082)	541	183	358
Proposed Sample Size (N=1200)	**600**	**200**	**400**
Proposed Randomization Ratios	**3**	**1**	**2**

It is not anticipated that additional subjects will be required, however if a subject drops out before the biopsy procedure they may be replaced as described in section 5.8.1.6.

5.9.3 Level of significance and power of the clinical investigation

Assuming a csPCa detection rate of 43% in each group, 1082 subjects are needed for 90% power to demonstrate that the lower bound of the two-sided 95% confidence interval is greater than the 10% non-inferiority threshold.

R and/or MATLAB software were used for sample size calculations.

5.9.4 Expected drop-out rates

Factors affecting possible drop-out rates include the option to withdraw participation at any time.

It is anticipated that a subject's inclination to withdraw at procedure-time will be minimal, as prostate biopsy is indicated clinically.

5.9.5 Pass/fail criteria

The primary outcome of the study will fail if the number of subjects diagnosed with csPCa is more than 10% lower than the number of subjects diagnosed with csPCa in the MRI/US arm. This will be quantified by testing against the lower two-sided 95% confidence interval bound for the difference.

5.9.6 Criteria for the termination of the clinical investigation

The investigation may stop early for success if the primary objective if proven with $p<0.0026$ at an interim analysis performed at 50% recruitment. This was calculated using O'Brien-Fleming bounds, and lowers the maximum p-value at final analysis from 0.025 to 0.024.

If the investigation is terminated early, no follow-up with subjects is required, since the standard of care for patients anticipating prostate biopsy is not affected by early termination.

5.9.7 Procedures for reporting deviation from the statistical plan

Where the analysis of case data does not handle unexpected data, Exact Imaging in conjunction with the Principal Investigators and 3rd party biostatistician will establish a strategy to modify the analysis algorithm and apply it to all data. Such modifications will include validation of the algorithm prior to its acceptance for use.

These modifications will be updated and described in the CIP, and/or as in the final report (as appropriate) along with justification for them.

5.9.8 Specification of subgroups for analysis

A subgroup analysis is planned for men in the MicroUS arm of the study who deviate from protocol by having prior mpMRI available. This analysis will be used to demonstrate whether or not this group is consistent with the group of men in the MicroUS arm who are mpMRI naïve.

5.9.9 Procedures that take into account all data

Statistical analyses around study endpoints will not include data for subjects who are withdrawn (before or after their biopsy) or for whom the collected study data is incomplete.

5.9.10 Treatment of missing, unused data

If a study subject withdraws from the main trial prior to imaging, his consent form will be retained, and the reason for exclusion of the data will be handwritten on the form as "withdrawn prior to imaging". Similarly, if a study subject withdraws from the main trial following his imaging, his consent form and CRF will be retained, and both will be marked "withdrawn following imaging".

This will allow data to be collected about the number of patients that withdrew from the investigation prior to the imaging procedure, and the number that withdrew after the procedure.

The same process will be applied to any circumstance of incomplete or incorrect data, with an indicator handwritten on his consent form and CRF to provide information about why the record is not used for analysis.

5.9.11 Exclusion of data

Conditions that would result in the exclusion of data would be if any data verification activity showed that data was recorded on the CRF incorrectly, or if the pathology report showed any inconsistency with information on the CRF.

If such incorrect data was discovered, data for this subject will not be included in any analysis, and the CRF for the subject will be marked to indicate that the data is excluded.

5.9.12 Subjects at multi-center investigations

This information is provided in section 5.8.3.7.

5.10 Data Management

Data will be stored on electronic CRFs using an Electronic Data Capture system, and exported to an analysis tool (Excel by Microsoft and/or MATLAB by Mathworks Inc.).

No subject-identifiable information will be transferred. Instead, study data pertaining to a particular subject will be entered using a de-identified alphanumeric subject code. This is described further in section 5.8.7.

Analysis data will be backed-up in accordance with Exact Imaging's standard operating procedures.

5.10.1 Data review

Source data will be verified by the Study Monitor, as described in section 5.8.5.1.

5.10.2 Data verification and validation

Source data will be recorded in the Electronic Data Base and/or on case report forms (CRFs) as described in section 5.8.6.

Source data will be verified by the Study Monitor, as described in section 5.8.5.1.

This data will be collected by the Study Coordinator or Study Monitor (collect de-identified films), and forwarded to Exact Imaging personnel for analysis. The accuracy of the data will be verified by Exact Imaging by manual comparisons between:

- data on CRFs and on images stored on ExactVu

5.10.3 Data retention

All documents related to this investigation will be handled in accordance with Exact Imaging's quality system procedure *QSP 4.2.3 Control of Documents*. This procedure describes the way Exact Imaging controls its documents in a way that involves a formal document review, approval and release process, and prevents outdated or obsolete documents from being used. This procedure is designed to comply with the requirements of ISO 13485.

Exact Imaging, and each Site Principal Investigator shall maintain the records collected during the investigation for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required

for purposes of supporting a premarket approval application. Institutions will retain data collected according to local institutional or applicable requirements of the Ethics Board/IRB.

5.10.4 Clinical quality assurance

This CIP identifies the elements of quality control principles that Exact Imaging applies to this clinical investigation, including the descriptions of procedures that ensure the clinical investigation is designed, conducted and monitored in accordance with applicable regulations and the requirements of the Ethics Board/IRB.

Exact Imaging maintains records to document the agreement of all parties involved in the investigation to the contents of this CIP.

5.11 Amendments to the CIP

All amendments to the CIP shall be agreed to between Exact Imaging and the study principal investigator and be recorded with a justification for the amendments. Deviations will be reviewed to determine the need to amend the CIP or to terminate the investigation.

When there are changes to the initial list of clinical investigators this list will not be formally updated by amendments at each change; Exact Imaging will maintain an updated list which will be available on request. The Ethics Board/IRB will be notified when required.

5.12 Deviations from the CIP

Investigators are not allowed to deviate from the CIP, except when the deviation is required to address the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation. Any deviation from the CIP (this document) shall be recorded together with an explanation for the deviation. Deviations shall be reported to Exact Imaging, who is responsible for analyzing them and assessing their significance with regards to risk and safety. The CIP will be amended when the nature of the deviation requires it to be.

The reasons for withdrawal and discontinuation of any subject from the investigation shall be recorded.

Deviations will be recorded in the final report along with the justification for the deviation. Where applicable, the Ethics Board/IRB will be notified.

5.13 Device Accountability

All devices used in this study are cleared for clinical use in the appropriate jurisdictions and are being used for their cleared indications. The devices used in this study are not hazardous and do not need any special procedures, particular materials nor any special instructions for the safe return after the clinical investigation is completed.

5.14 Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

This CIP and the investigation itself are designed to meet applicable requirements and regulations of the US FDA and other appropriate regulatory bodies for conducting clinical investigations.

The investigation will not begin until the required approval is obtained from the Ethics Board/IRB.

Any additional requirements imposed by the Ethics Board/IRB and/or the appropriate regulatory authority shall be followed

5.15 Informed Consent Process

This informed consent process is obtained by providing a potential study subject with an information sheet containing information about the purpose of the investigation, how to participate, benefits and risks, as well as information about the medical procedures to be performed. When a potential study subject signs the consent form, he agrees to enroll in the investigation. This clinical investigation does not involve emergency treatment where prior informed consent of the subject is not possible because of the subject's medical condition.

5.16 Adverse Events, Adverse device effects, and device deficiencies

5.16.1 Reporting adverse events

Unanticipated adverse device effects during clinical investigations of devices will be reported as appropriate to Exact Imaging, the Ethics Board/IRB and investigators participating in the study.

Exact Imaging will retain copies of adverse event reports as described in section 5.10.3.

5.16.1.1 Adverse event reporting process

Exact Imaging follows an internal company procedure, *Clinical Trial Incident Reporting Procedure*, to assess and report adverse events and other incidents associated with the investigation.

This process specified in this procedure is as follows:

1. An investigator will report any incident to Exact Imaging as soon as possible, and no later than 5 working days after first learning of the event.
2. Exact Imaging will conduct an evaluation of the incident, and determine the nature of the incident.
3. Exact Imaging will follow the process for reporting to the Ethics Board/IRB as required within the required timeframe, and in the required format.

5.16.1.2 Adverse event report format

Reports must follow the Ethics Board/IRB guidelines, and use the required reporting form.

5.16.1.3 Site Contacts

Site contact information is located on the individual site’s approved Informed Consent Form (as per their ethics committee) and Clinical Trial Agreement

5.16.2 Device deficiency reporting process

If a device deficiency does not require immediate resolution, it will be discussed between the principal investigator, Study Monitor and Exact Imaging during the appropriate site visit, and resolved as described in section 5.8.5.1.

If a device deficiency required immediate resolution, the principal investigator will report the issue to the Study Monitor and Exact Imaging by phone. The Study Monitor will assess the issue, and work with Exact Imaging personnel to provide a solution or workaround in the necessary timeframe.

5.16.3 Foreseeable adverse events

There are no foreseeable adverse events or adverse device effects related to the use of ExactVu in this investigation.

5.17 Vulnerable population

Considerations for vulnerable populations such as minors are not required, as the inclusion criteria related to age excludes this population automatically.

Considerations for vulnerable populations such as those with potentially limited comprehension of research methods are not required, as enrolled subjects would undergo prostate biopsy regardless of whether or not they participate in the investigation.

Considerations for vulnerable populations such as those with language or cultural barriers are not required, as enrolled subjects would undergo prostate biopsy regardless of whether or not they participate in the investigation, and it is assumed they would have taken steps to comprehend the contents of the Patient Information and Consent form prior to signing it.

Considerations for vulnerable populations such as those that are socially or economically disadvantaged that participation in medical research is viewed as the only option to access otherwise unavailable medical treatment are not required, as enrolled subjects would undergo prostate biopsy regardless of whether or not they participate in the investigation.

5.18 Suspension or premature termination of the clinical investigation

If patients are harmed in any way this trial will be halted until the cause is identified and measures taken to correct it. The Ethics Board/IRB and any other affected regulatory body will be notified in accordance with section 5.16.

In the event that the investigation is terminated early, Exact Imaging will collect case report form data for consideration towards future clinical investigations. The Ethics Board/IRB shall be informed promptly and provided with the reason(s) for the termination.

5.19 Publication policy

Exact Imaging encourages the investigators to publish the results of this clinical investigation to reputable journals.

The conditions by which the results may be published are:

- Investigators are required to advise Exact Imaging of their intention to publish an article related to the results of the investigation.
- Exact Imaging requires the opportunity to review any articles pertaining to the results of the study prior to publication.
- All Site Principal Investigators and Study Principal Investigator must provide consent, in writing, prior to manuscript submission.

No subject will be identifiable in any published results.

5.20 Critical Literature Review

(Literature reviewed July 28 2021)

Introduction and Objective
Significant data is available on both the effectiveness of standard of care mpMRI biopsy and micro-ultrasound biopsy. This critical literature review aims to analyze the available data on these techniques in order to estimate the detection rates of csPCa in this study and the difference in detection rate that would be clinically important.

Methodology
General
Clinical guidelines from the AUA, EAU, and NCCN were used as the starting point for this review. All relevant citations used in the acceptance of mpMRI as the recommended strategy for biopsy were reviewed.

The PubMed/Medline and Google Scholar databases were used to identify relevant literature on micro-ultrasound, in addition to unpublished data held by the manufacturer. Search terms included:

Prostate, Ultra High Resolution Ultrasound, High Frequency Ultrasound, High Resolution Ultrasound, micro-ultrasound, PRI-MUS

Selection criteria for documents
All relevant data from studies with similar procedure, inclusion and exclusion criteria will be included. Studies involving similar ultra-high resolution ultrasound devices will be included, as well as those using standard low resolution ultrasound. Where the results are still relevant to the review, deviations in procedure or inclusion will be discussed for each study or group of studies.

Critical evaluation of literature
The most common technique for diagnosis of prostate cancer involves screening based on prostate specific antigen (PSA), followed by systematically spacing biopsy samples throughout the gland in men at risk. Unfortunately, this systematic biopsy procedure has a sensitivity of only 48% to detect clinically significant prostate cancer (csPCa) compared to template mapping biopsy[4], and a 30% rate of underestimating the risk profile of the cancer when it is found[14]. Men undergoing this systematic biopsy pathway are at risk of underdiagnosis, resulting in a delay to appropriate treatment, increased risk of prostate cancer mortality, and an unnecessary exposure to the morbidity of repeat biopsy.[15–17] While various strategies including both advanced imaging and biomarkers are available to refine the population exposed to biopsy-related morbidity, improved biopsy guidance is necessary to ensure these men receive appropriate therapy matched to the true aggressiveness of their disease.
Multiparametric MRI (mpMRI) targeted biopsy has been extensively studied as a solution to this problem and represents a clear improvement over systematic biopsy.[18–21] According to a

Cochrane review on the subject, the addition of mpMRI targeting improved detection of csPCa by 5% over systematic biopsy in biopsy naïve men.[22] A meta-analysis by Goldberg showed a greater impact with a 7-18% improvement.[23] Similar reductions in upgrading have also been demonstrated, lowering the upgrading rate on radical prostatectomy from 30% to 6.7%.[14]

Table 1 - Efficacy of additional mpMRI-directed samples over Systematic biopsy alone. Improvement in csPca detection ranges from 5% to 18% while overall detection rate ranges from 30%-61%.

Study	MRI+Sys csPCa	Sys csPCa	Difference	Limitations
Cochrane meta-analysis[22]	53%	48%	5%	
Goldberg et al. meta-analysis[23]	N/A	N/A	7-18% (11% in RCTs)	
Valerio et al. meta-analysis[24]	36%	26%	9%	Variability in csPCa definition and inclusion of prior neg biopsy
Kasivisvanathan et al. meta-analysis[25]	40%	27%	12%	Variability in csPCa definition and inclusion of prior neg biopsy
PRECISE[26]	35%	30%	5%	Targeted biopsy only on MRI
MRI-FIRST[18]	37%	30%	7%	
PAIREDCAP[27]	61%	52%	9%	
PRECISION[28]	38%	26%	12%	No systematic samples in MRI group
PROMIS[4]	37%	22%	15%	No MRI targeted biopsy
4M[21]	30%	23%	7%	In-bore MRI sampling rather than MRI/US fusion
ASIST[29]	33%	27%	6%	Active Surveillance population

The mpMRI-informed diagnostic pathway

The American Urology Association, European Association of Urology, and National Comprehensive Cancer Network all recognize the use of mpMRI in order to improve the efficacy of the prostate biopsy procedure.[30–32] However, mpMRI targeted biopsy still misses small high grade cancers and up to 20% of GG2 cancers[4,18,20]. These groups agree that mpMRI targeted biopsy should be combined with systematic biopsy in order to optimize the procedure, and that systematic biopsy should still be performed in the event of negative mpMRI but persistent clinical suspicion of cancer.

The inclusion of mpMRI has altered the diagnostic pathway by requiring a cohort of expert radiologists specializing in prostate MRI to meet the demand. The care pathway has also required changes to include referral to radiology after (and, in some settings, before) initial consultation with the urologist.

These changes to the patient care pathway have introduced new sources of error and delayed diagnosis in many places. In the UK for example, the median time to diagnosis is 55.5 days.[33] At one prostate diagnostic clinic, the time-to-diagnosis was significantly lower in patients who did not receive mpMRI compared to those that did (15 vs. 22 days).[33] This discrepancy is greater in centers which have pre-existing resource constraints.

Variability in care has been exacerbated by the reliance on mpMRI due to significant and wide-spread inter-reader variability. Pickersgill et al. found poor agreement and poor accuracy among blinded radiologists for PI-RADS score and prediction of csPCa.[34] Similarly, Westphalen et al. found a large 27%–44% variability in the targeted detection rate (positive predictive value) of MRI-targeted biopsy across 24 imaging centers.[35] This increase in variability reduces confidence in the diagnostic process and may contribute to suboptimal results as mpMRI adoption increases. In the same way, the inclusion of MRI-derived data, along with the transfer of imaging data in pre-specified proprietary formats for fusion biopsy, adds complexity to the diagnostic pathway.

This represents a source of error. The magnitude of this error has yet not been well quantified, but is likely to be substantial outside recognized centers of excellence.
Further, mpMRI cannot be used in all men. Among the contraindications are several conditions that are prevalent within the population at risk, including implanted devices such as pacemakers and hip replacements (hip prostheses alone represent up to 4%[36]), impaired kidney function (12%[37]), and claustrophobia (3-5%[38]). These men are not candidates for the mpMRI diagnostic pathway.

Micro-ultrasound imaging
Micro-ultrasound (microUS) is a recently developed, real-time ultrasound-based modality operating at 29MHz compared to Conventional trans-rectal ultrasound systems at 6-9MHz. Thus microUS results in a significantly higher resolution, 70 microns, which allows the underlying tissue structure to be visualized.[1,39,40] At a resolution of 70 microns, alterations in ductal anatomy associated with higher grade cancer can be visualized, based on the same principle as restricted diffusion with MRI.
Images are interpreted according to the PRI-MUS protocol (Figure 1). This evidence-based risk scale was initially validated[5] in 2016, and a larger scale, prospective validation study[41] confirmed these results in 2019. The PRI-MUS protocol has similar risk stratification to the PI-RADS system for MRI.[11]

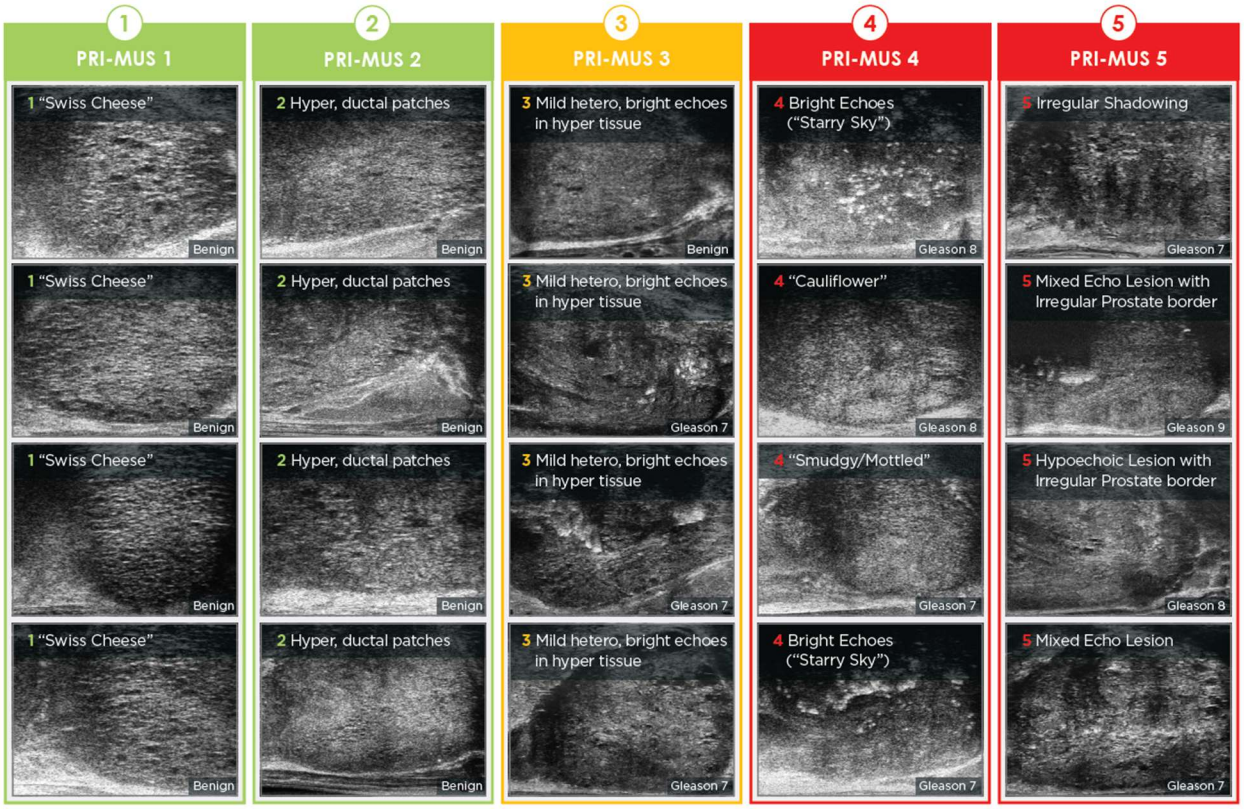


Figure 1 - Example images demonstrating the various imaging features of the PRI-MUS protocol. This risk-stratification protocol grades images based on tissue patterns seen in micro-ultrasound from 1 (very low risk fo significant cancer) to 5 (very high risk of significant cancer).

Micro-ultrasound and mpMRI fusion biopsy
Due to the challenges of performing biopsy within the MRI gantry, MRI/US fusion biopsy is the more popular approach to sample targets identified by mpMRI. However, aligning the mpMRI

data which is often taken on a different day and with the patient in a different position to the real-time ultrasound is not trivial and may be complicated by pressure from the ultrasound transducer on the prostate causing deformation. This procedure relies heavily on two factors to achieve accurate sampling: reliable position tracking and correction for soft tissue deformation.
Micro-ultrasound has been hypothesized to improve the accuracy of mpMRI fusion biopsy by reducing the operator's reliance on the position tracking and deformation calculations of their fusion platform. Since micro-ultrasound is able to observe the majority of these suspicious areas natively, the operator is able to sample under direct real-time visual guidance rather than relying on the accuracy of the fused MRI images, or any pre-defined contouring. This has been investigated by several groups (see Table 1Table 2), with Cornud et al. demonstrating that microUS was able to visualize 79% of all MRI targets natively and 100% of targets positive for csPCa.[42] Perhaps because of this, Claros et al. reported a 15% improvement in MRI-directed biopsy yield when comparing a robotic fusion platform with a microUS platform.[43]
Micro-ultrasound may also find additional suspicious regions within the prostate, and these targets may further improve biopsy yields when added to the mpMRI fusion biopsy strategy. This has been demonstrated by several groups, showing additional detection of csPCa in the 1-17% range (Table 2).
Improving the accuracy of mpMRI-target sampling, removing contouring requirements, and finding additional targets that may have been missed on mpMRI would mitigate the complexity and variability in the mpMRI pathway.

Table 2 - Recent studies adding microUS to mpMRI protocols

Study	Improvement
Cornud et al.[42]	79% of all mpMRI targets visualized, including 100% of csPCa targets.
Claros et al.[43]	15% improvement in MRI-targeted biopsy csPCa rate
Wiemer et al.[12]	17% added csPCa due to microUS targeted samples
Lughezzani et al.[11]	1% added csPCa due to microUS targeted samples
Socarrás et al.[44]	6% added csPCa due to microUS targeted samples

Can micro-ultrasound avoid mpMRI fusion biopsy?
In order to simplify the diagnostic pathway further, it would be desirable to replace mpMRI with a real-time modality of equal clinical utility. This change would improve time to diagnosis, as well as access, by combining the imaging and biopsy steps. In order for such a pathway to be acceptable it should maintain the accuracy of the mpMRI pathway for the detection of csPCa.
Data available (see Table 3) on this topic include a large 11-center, 1040-subject registry study performing a direct comparison to mpMRI which concluded that the two techniques provided similar sensitivity and negative predictive value.[13] Various other single-center studies and meta-analyses have demonstrated similar rates of csPCa detection between mpMRI-guided and microUS-guided biopsy protocols.[8,11,12,39,45,46]

Table 3 - Recent studies comparing microUS and mpMRI

Study	Metric	MRI	MicroUS
Klotz et al.[13]	Sensitivity	90%	94%
Wiemer et al.[12]	csPCa detection	38%	44%
Lughezzani et al.[11]	csPCa detection	35%	35%
Socarrás et al.[45]	csPCa detection	28%	24%
Abouassaly et al.[8]	Increase in csPCa detection	N/A	12%

Calculation of Non-Inferiority Threshold and Expected Detection Rates

The non-inferiority threshold of 10% was determined by expert-consensus from the advisory panel involved in the creation of this protocol, however it is consistent with the improvement in csPCa rates observed in the literature for mpMRI over the previous standard of systematic biopsy (see Table 1). The expected csPCa rates across the three arms of 42-44% were calculated based on pooled data from 414 biopsy naïve subjects with combined microUS and mpMRI biopsy across 4 studies at 7 institutions. This data includes 1 previously published study[11] and 3 studies which have been submitted for publication, and correlates well with the data from Table 1.

Evaluation of hazards, risks and safety measures
Risks associated with the biopsy procedure are well understood and outside the scope of this protocol since the biopsy procedure is clinically indicated and study procedures are not expected to modify these risks. Risks associated with study data collection will be managed by the Study Monitor, as described in this CIP.

Statistical and weighting methods
All clinical studies were weighted based on enrollment numbers, unless otherwise stated or specifically excluded for differences in protocol or enrollment. Care was taken to identify studies with patients drawn from the same population which would not be independent.

Conclusions
Micro-US is a promising modality for TRUS-guided biopsy procedures which may offer improved workflow, reduced complexity in care pathway, reduced time-to-diagnosis, and reduced healthcare costs. Enrolment numbers are reasonable and consistent with other human studies in this area.

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Appendix A Sponsor Responsibilities

Clinical quality assurance and quality control

Quality assurance and quality control principles shall apply to the processes of the clinical investigation. The sponsor shall:

a. implement and maintain written clinical quality procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with ISO 14155, the CIP, any subsequent amendment(s), and any other applicable standards and regulatory requirements
b. maintain records to document the compliance of all parties involved in the clinical investigation
c. ensure that the auditing requirements are met when applicable
d. justify and document significant exceptions to the requirements identified in ISO 14155

Selection of clinical personnel

Prior to commencement of the clinical investigation, the sponsor shall:

a. define, establish and allocate all the roles and responsibilities related to the clinical investigation in one or more written agreements
b. select an appropriately qualified Principal Investigator
c. receive disclosures of conflict of interest from principal investigators and investigators, where required by national regulations
d. ensure the members of the investigation site team and their designated authorization(s) are identified in a log with details
e. designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitor(s)
f. ensure documentation of training, experience and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical investigation, including training, on
    a. the use of the investigational device(s)
    b. device accountability procedures
    c. Investigator's Brochure (same as Clinical Investigator Protocol)
    d. CIP
    e. CRFs and instructions for completion
    f. the written informed consent form and process as well as other written information provided to subjects
    g. sponsor's written procedures, ISO 14155 and any applicable regulatory requirements
g. ensure that any clinical-investigation-related activities of sponsor representative(s) at the investigation site(s) are described in the CIP and the informed consent form, and that these activities occur in such a way that they do not bias the data integrity

NOTE Individuals such as field engineers or sales representatives who will provide technical expertise in the implementation of the clinical investigation, are examples of sponsor representatives

h. consider the need for a data monitoring committee and, if appropriate, establish the committee

Preparation of documents and materials

Prior to commencement of the clinical investigation, the sponsor shall:

a. prepare required documents and ensure they are approved by the relevant persons by dated signature; if required, copies shall be provided to all parties involved, and dated signatures obtained as appropriate
b. ensure that a supply of investigational devices is available in a timely manner for the clinical investigation; investigational devices shall not be made available to the principal investigator until all requirements to start the clinical investigation are met
c. provide insurance covering the cost of treatment of subjects in the event of clinical-investigation-related injuries, in accordance with the national regulations if applicable,
d. document any financial arrangements between the principal investigator or the investigation site and the sponsor
e. submit any required application(s) to begin the clinical investigation in a given country to the appropriate regulatory authority(ies) for review, acceptance or permission [as per applicable regulatory requirement(s)]
f. ensure that the Ethics Board/IRB approval/favourable opinion is obtained and documented, and that appropriate provisions are made to meet any conditions imposed by the Ethics Board/IRB
g. ensure that any modification(s) required by Ethics Board/IRB or regulatory authority are made and documented by the Principal Investigator and have gained the approval/favourable opinion of the Ethics Board/IRB or regulatory authority

Conduct of clinical investigation

The sponsor shall be responsible for:

a. accountability of investigational devices throughout the clinical investigation,
b. documenting correspondence with all parties involved in the clinical investigation, including the Ethics Board/IRB and regulatory authorities
c. ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation
d. reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s)
e. taking prompt action to secure compliance with all clinical investigation requirements
f. submitting progress reports, including safety summary and deviations, when requested, to Ethics Board/IRB and any other regulatory authorities

Clinical investigation close-out

The sponsor shall:

a. ensure all clinical investigation close-out activities are properly conducted
b. provide a statistical analysis of the data
c. produce a clinical investigation report and submit it for review
d. ensure that the clinical investigation report, whether for a completed or prematurely terminated clinical investigation, is provided to Ethics Board/IRB, participating investigators and regulatory authorities, as required by national regulations

Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation data shall reside with the sponsor. All requirements in ISO 14155 applying to a sponsor shall also apply to the external organization inasmuch as this organization assumes the clinical-investigation-related duties and functions of the sponsor.

The sponsor shall specify in writing any clinical-investigation-related duty or function assumed by the external organization, retaining any clinical-investigation-related duties and functions not specifically transferred to, and assumed by, the external organization.

The sponsor shall be responsible for verifying the existence of and adherence to written procedures at the external organization.

Communication with regulatory authorities

The sponsor shall, if required

a. notify or obtain approval from regulatory authorities in the country where the clinical investigation is conducted
b. report on the progress and status of the clinical investigation
c. perform safety reporting