Clinical Investigation Plan and Study Protocol for Urology San Antonio MRI/MicroUS Comparison (EVU-2018-001)

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Approvals	Signature	Date
Sponsor (Exact Imaging)		
Dr. David R. Talley (Urology San Antonio)		
Dr. Michael A. White (Urology San Antonio)		

Revision History

Date	Author	Rev	Description of Change
19 June 2018	B. Wodlinger	1.0	Initial revision to submit to WIRB
3 July 2018	B. Wodlinger	1.1	Revised with comments from Dr. Talley
5 July 2018	B. Wodlinger	1.2	Revised statistical plan to account for positive MRI biopsy only

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List of Appendices

1 Purpose

The purpose of this Clinical Investigation Plan and Study Protocol (CIP) is to present information for the *Urology San Antonio MRI/Micro-US Comparison* 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 Exact Imaging 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 of 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 falls under normal FDA parameters.

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.* *NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.*

Term	Definition
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 appointed by the sponsor 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 to the sponsor 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 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 14155:2011 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. 21 CFR Part 812 Subpart B – Investigational Device Exemptions
4. Guidance for Industry and FDA Staff - Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers

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 in the United States at Urology San Antonio.

Exact Imaging and the principal clinical 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 Urology San Antonio or its reviewing research ethics board (Western IRB).

In the event that Exact Imaging decides that any requirement given in sections 5.3 through 5.20 is not applicable, relevant or appropriate, a clear statement justifying the omission of the information specified shall be provided on each occasion.

5.3 General information

5.3.1 Identification of the CIP

The title for the clinical investigation is *Urology San Antonio MRI/Micro-US Comparison Study*.

The revision number and date of the document are indicated in the Revision History. The Exact Imaging identifier for the investigation is *EVU-2018-001*.

5.3.2 Identification of the sponsor

The sponsor for the clinical investigation is:

Exact Imaging Inc.
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5.3.3 Identification of the investigators

Co-Principal Investigators

Name	David R. Talley
Professional position(s)	Urologist
Name	Michael A. White
Professional position(s)	Urologist

Study Coordinator

Name	Manuel Hernandez
Professional position(s)	Director of Research

Address of the Institution(s)

5.3.4 Overview of the investigational protocol

The investigational protocol describes a study designed to compare ultra-high resolution transrectal micro-ultrasound (micro-US), and multi-parametric MRI (mpMRI). These modalities are both used clinically to identify targets for prostate biopsy, however little data is available to compare their sensitivity. While mpMRI is used clinically to identify targets for biopsy, it is not used for real-time biopsy guidance due to challenges performing the biopsy procedure within the MRI gantry. Instead, targets identified on mpMRI are sampled during transrectal ultrasound guided biopsy as part of the prostate biopsy procedure, often using software assisted fusion products. For this investigation, the biopsy procedure will be guided by transrectal micro-US (current standard of care at Urology San Antonio), and will include systematic (standard, random, extended sextant) plus image-guided prostate biopsies among men with clinical suspicion of prostate cancer and an indication for prostate biopsy. The FusionVu software-assisted fusion feature will be used to sample mpMRI targets.

This investigation furthers two cohort studies which demonstrate similar or superior sensitivity for micro-US over mpMRI from two centers in Europe.[1,2] This study will provide the first prospective blinded confirmation of these results.

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.[3] Two other previous studies have been approved through WIRB, including protocol 20131849

which provided the first randomized clinical trial on micro-US and WIRB protocol 20162036 which provided a small initial case series comparison of mpMRI and micro-ultrasound in the active surveillance population. Results from both studies were positive and have recently been presented.[4,5]

Details about objectives of the investigation are described provided in section 5.7.1. The investigational protocol was developed by Exact Imaging, in consultation with Dr. Talley and Dr. White (Urology San Antonio), and will be followed by the investigative team. Exact Imaging is responsible for the contents of the investigational protocol, and for monitoring the investigation.

5.4 Device Description

The ExactVu device is a new commercialized 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 the software version intended for the investigation received pre-market clearance on April 30th 2018 for the following indications for use:
The ExactVu High Resolution Micro-Ultrasound System is intended for use by qualified medical professionals for diagnostic ultrasound imaging or fluid flow analysis of the human body; the intended uses are: Small Organ (prostate), Transrectal. The system may be used with patients of all ages, but is not designed for pediatric or fetal use.

The unique features of ExactVu are:

- The ability to scan using high-resolution (micro-US) and conventional transducers (on the same platform without disconnecting either transducer
- The ability to import and overlay MR data with micro-US images to support image guidance
- Custom keyboard layout tailored to this application
- High-frequency imaging:
  - The ability to leverage high-resolution imaging to target biopsies in the appropriate quadrant(s) at visibly suspicious regions
  - Transducer array and housing designed specifically for prostate imaging
  - Increased image resolution inherent in its design (as compared to conventional ultrasound systems currently available)
  - 21 MHz center frequency (i.e., B-Mode)
  - High performance 512 element transducer
  - RF electronics designed and optimized for ultrasound at high frequency

ExactVu is operated using the keyboard interface, and menu options in the software user interface. The keyboard provides an integrated trackball, which is used to access the menu options. Controls are provided for all typical elements of an ultrasound exam of the prostate, with or without a biopsy procedure, including:

- Management of patient and exam information
- Study types (prostate biopsy)
- Start and stop data acquisition
- Adjust imaging and display settings
- Save images and review previously saved images
- Measure structures and add comments to acquired data
- Display overlays (measurements, annotations, needle guide overlay)

- Print acquired and previously saved images

Onscreen feedback is provided to users to provide information regarding the outcome of user actions, and includes status bar messages and confirmation messages for data edits.

5.4.1 Device Identification

Ultrasound System	ExactVu™ high resolution micro-ultrasound system
	Serial Number: 6437180005
High-Frequency Transducers (micro-US)	29 MHz High Resolution Transrectal Side-fire Transducers (Linear)
	Serial Number: 6089170044
	Serial Number: 6089170045

5.4.2 Purpose of the device in the context of the investigation

For this investigation, ExactVu will be used to perform the following tasks:

- Using the high-resolution transducer, image the prostate and guide a biopsy needle to physician-selected areas of the prostate
- Using the FusionVu software feature to provide software-assisted fusion of mpMRI images to guide a biopsy needle to physician-selected areas of the prostate
- Store images of the location where biopsy samples were taken
- Provide tools to identify and measure regions of interest

It will be used for procedures with men between 40 and 79 years of age who are scheduled for a prostate biopsy.

5.4.3 Materials that contact the patient

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

During use, the transducer 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 Biopsy needle construction materials

The biopsy needle will be an off-the-shelf product of gauge size 18, and selected by the investigator who will use it.

5.4.3.4 Qualified Gels

Exact Imaging follows 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).

ExactVu is designed to introduce no increased risk when compared to conventional ultrasound, and as such, Exact Imaging accepts Urology San Antonio may have approved institutional protocols that call for the use of non-sterile gel for transrectal 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, Exact Imaging recommends the use of single-dose gels.

5.4.3.5 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.

5.4.3.6 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

5.4.4 Instructions for use

Instructions for use for ExactVu and its accessories are provided in ExactVu labeling, as identified in section 5.8.4.2.

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 Urology San Antonio 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 50 cases. The investigators and personnel at Urology San Antonio are also already familiar with the FusionVu software feature, having used it to sample mpMRI-targets under micro-ultrasound guidance on more than 10 cases.

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.

Radiologists reading the mpMRI studies must provide PI-RADS v2 reports, and as such must have received training in the PI-RADS v2 protocol. Evidence of this training is to be provided by Urology San Antonio and their radiology partners.

5.4.6 Medical procedures

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

Prior to consent and biopsy, the subject will have been imaged using mpMRI according to the PI-RADS v2 protocol, per the inclusion criteria and standard of care. The radiologist's report must be completed before the biopsy procedure.

The detailed procedure is as follows:

1. Screening and consent visit
2. Biopsy visit:
    a. Operator 1 (blinded to mpMRI images and report)
        i. Administer IV sedation per site standard of care
        ii. Scan with EV29L micro-ultrasound transducer (ExactVu system)
        iii. Save sweep of prostate
        iv. Record any suspicious regions (PRI-MUS 3+)
        v. Measure prostate volume (optional)
        vi. Targeted biopsy samples (from micro-ultrasound)
            1. Samples from each targeted lesion will be placed in a separate labeled jar to ensure they can be independently discussed on the pathology report
        vii. Systematic biopsy samples (fill in up to 12 samples)
    b. Operator 2 (unblinded to mpMRI images and report)
        i. Align labeled mpMRI sequences with ultrasound using FusionVu software
        ii. Save a full sagittal sweep through the prostate with mpMRI guidance active for retrospective evaluation
        iii. Targeted biopsy samples (using mpMRI guidance)
            1. Samples from each targeted lesion will be placed in a separate labeled jar to ensure they can be independently discussed on the pathology report

c. Remove transducer, use site-specific standard post-biopsy follow-up

The biopsy procedure takes approximately 30 minutes. The subject is not required to come for additional clinic visits in the context of the study.

Biopsy results will be provided to the subject's physician as per standard of care. Further healthcare decisions and follow-up are outside the scope of this study. The subject's participation in the study is completed following the prostate biopsy.

5.5 Justification for the Design

Conventional-ultrasound guided prostate biopsies are the most common clinical procedure used for detection of prostate cancer. This technique involves sampling each sextant area of the prostate with one or more needles, with attention to sampling any suspicious hypoechoic lesions in these or other areas of the prostate.

However, conventional-ultrasound does not reliably image cancerous lesions within the prostate, and at least 75% of the time identifies no abnormalities consistent with cancer even in men known to have prostate cancer. Instead, conventional-ultrasound is generally simply used to identify the prostate and help guide systematic 12-core biopsies for the detection of prostate cancer and for the monitoring of prostate cancer in men on active surveillance. The inability to accurately image prostate cancer results in numerous unnecessary biopsies which have associated patient morbidity and increased health care costs[6].

Improvements in prostate cancer imaging are clearly needed.

mpMRI has been suggested as a means to improve prostate cancer imaging, however this modality may not provide adequate visualization of small lesions due to the poor resolution of mpMRI. Further, a specialized radiologist is required to interpret the imaging and real-time image-guidance is not possible. For these reasons, an office-based real-time imaging solution would be preferred.

micro-US 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)[7]. 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[3]. More recent studies have extended these findings, by providing further evidence of the superiority of micro-US to conventional-ultrasound[4] and preliminary evidence that micro-US may provide similar improvements to mpMRI.[1,2,5]

The proposed study will allow direct imaging comparison within the same patient between mpMRI and micro-US to directly compare the sensitivities of these two modalities to prostate cancer.

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 significant 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*[3].

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[4]. 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.[5,8]

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.[1] 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[2] 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%.

5.5.2.5 Literature review

A critical literature review was performed to establishing incidence, prevalence and cancer detection rates, as further justification for the design of the proposed investigation. 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

5.6.1 Device risk analysis and management

The Risk Management Plan for ExactVu and the related hazard analysis was conducted in accordance with ISO 14971 and with reference to Exact Imaging's quality system procedures.

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 biopsy procedure.

There are some known risks and discomforts associated with a biopsy procedure, however no new risks are introduced by participating in this trial, nor by the use of ExactVu, and known risks are not increased.

Known risks and discomforts associated with biopsy of the prostate include:

- Pain in the biopsy area (rectum area)
- Sudden, complete inability to urinate
- Dysuria (difficulty with urination)
- Urinary tract infection (UTI)
- Prostatitis (infection of the prostate)
- Sepsis (severe whole body infection)

- Hematospermia (blood in the semen or ejaculation fluid)
- Hematuria (blood in the urine)
- Hematochezia (blood in the stool)
- Allergic reaction to lidocaine

There are also known risks and discomforts associated with the MRI procedure, however no new risks are introduced by participating in this trial, and these known risks are not increased. The subjects included in the research will have already received mpMRI as standard of care before enrollment. Known risks and discomforts associated with mpMRI include:

- Allergic reaction to contrast agent (gadolinium chelate)
- Nephrogenic systemic fibrosis due to contrast agent (gadolinium chelate)
- Anxiety due to the confined space
- Tissue burns or damage due to undisclosed presence of metallic implant

5.6.3 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 biopsy procedure clinically. ExactVu is designed to introduce no increased risk when compared to conventional ultrasound. An enrolled study subject has already been scheduled for prostate biopsy by his physician.

5.7 Objectives and Hypothesis

5.7.1 Objectives

Primary Outcome: Comparison of subject-level detection rate of clinically significant cancer (csPCa, defined as ISUP 2 or higher) between micro-ultrasound targeted biopsy and mpMRI targeted biopsy.

Secondary (unpowered) Outcomes:

- Compare lesion size and shape between mpMRI and micro-ultrasound (follow-up with detailed whole-mount pathology when available)
- Compare detailed pathological findings (cribiform structure, density of cancer, subtype of cancer) with imaging findings in both modalities
- Identify percentage of micro-ultrasound lesions (with positive biopsy result) that can be identified retrospectively using mpMRI (requires retrospective re-reading of mpMRI sequences given list of micro-ultrasound targets)
- Identify percentage of mpMRI lesions (with positive biopsy result) that can be identified retrospectively using micro-ultrasound (requires retrospective re-reading of micro-ultrasound sweeps given list of mpMRI targets)

5.7.2 Hypothesis

Primary Hypothesis: Micro-ultrasound provides non-inferior (10% margin) sensitivity to detect csPCa using targeted samples compared to mpMRI.

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

All subjects will receive standard routine care (i.e., prostate biopsy) per standard indications, using transrectal ultrasound guidance. Micro-US can reliably image the peripheral zone of the prostate. This is done in a transrectal approach, as is conventional ultrasound.

5.8.1 General

5.8.1.1 Type of clinical investigation

The investigation is a study where all subjects have an indication for prostate biopsy. This will allow the most general assessment of the study's main objective which is comparing the imaging quality of micro-US with mpMRI. Each subject will act as their own control in order to make the resulting images as comparable as possible. This multiple-imaging design also reduces the number of subjects needed without substantially increasing risk, subject discomfort, or procedure time.

5.8.1.2 Avoiding bias

The mpMRI report will be blinded from Operator 1 performing the micro-ultrasound targeted and systematic biopsies, to avoid biasing identification of suspicious regions on micro-US. Operator 2 will have full knowledge of the mpMRI report and images, but will not observe the micro-ultrasound targeting portion of the procedure or see the resulting target locations. Separate operators will complete the two phases of the procedure to avoid bias from the micro-ultrasound targets interfering with biopsy site selection for mpMRI targets.

5.8.1.3 Endpoints

Primary endpoint
The primary endpoint is the presence of clinically significant prostate cancer (csPCa) in each subject. The per-subject presence of cancer will be determined based on a positive biopsy from any sample, targeted or systematic. Patient-level sensitivity for a given imaging modality will be determined through systematic biopsy results plus targeted samples taken using only that modality. In this way we approximate clinical reality of using a given modality for systematic plus targeted biopsy.

Secondary endpoints
Sensitivity of targeted-only samples for each modality will also be calculated in order to determine the effectiveness of a targeted only biopsy technique in each case. Presence of cancer per-target will also be assessed, along with detailed pathological findings, and targeting modality identifying the lesion. Size and shape of lesions will also be recorded from recorded images.

5.8.1.4 Variables

The sensitivity, specificity and area under the ROC curve for accurate identification of clinically significant prostate cancer for each modality will be determined, along with the corresponding credible intervals. Summary statistics will be provided for all modalities.

Biopsy results may fall into 4 categories based on pathology review:

1. Clinically significant cancer (GS > 6)
2. Clinically insignificant cancer (GS = 6)
3. Cancer precursors (HGPIN, Atypia)
4. Benign (including findings of Prostatitis)

Distribution of findings for all categories, and comparison of these distributions between modalities will also be reported.

5.8.1.5 Assessing variables

The analysis to be performed on data collected during the investigation will be done on software customized and validated by Exact Imaging. This software will be maintained as per Exact Imaging's internal operating procedures. 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.

A third-party statistician will be contracted to independently confirm all results.

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 his biopsy procedure, and because it is not expected that a subject will drop-out after his biopsy procedure, the need to replace subjects is expected to be unlikely.

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

5.8.2 Medical devices and comparators

The ExactVu micro-ultrasound system with high-frequency EV29L transducer will be used. The FusionVu software package will be used for software assistance during mpMRI-US fusion. This device, including all software and hardware components are cleared by FDA for the prostate biopsy and mpMRI fusion biopsy procedure in the United States.

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 presenting for prostate biopsy due to clinical suspicion of prostate cancer
2. 40-75 years old
3. Available mpMRI images and report, performed according to the PI-RADS v2 standard

Patients who choose not to participate will be offered a standard of care prostate biopsy. No patient will be denied appropriate medical care based on their willingness to participate in this trial.

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. Men with anorectal abnormalities preventing TRUS-guided prostate biopsy
2. Men who are unable to provide their own informed consent
3. Prostate volume on MRI > 100cc

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 biopsy 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.

NOTE: Informed consent documentation will be provided in English for potential subjects.

5.8.3.5 Total expected duration of the clinical investigation

The investigation is expected to take approximately 12 months maximum.

5.8.3.6 Expected duration of each subject's participation

The procedure follows the standard of care, in that a prostate biopsy is performed. Subjects are not required to come for additional clinic visits in the context of the investigation.

Participating in the trial will add approximately 5-10 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 120.

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

The investigation is expected to take approximately 12 months in total. This is intended to provide Urology San Antonio with adequate time to enroll and study the projected number of subjects in the trial. A subject’s participation in the investigation is completed following his prostate 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

Exact Imaging's responsibilities as the sponsor of this clinical investigation include the preparation of this CIP. These responsibilities are presented in detail, to facilitate planning of this investigation.

Exact Imaging will supply Urology San Antonio with:
- Sterile needle guides and transducer sheaths required for biopsy procedures to be performed on the ExactVu system
- Exact Imaging will not provide biopsy needles, a biopsy gun (if used), surgical gloves or gel, an ExactVu system, or EV29L transducer

Exact Imaging will fund the study, 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 biopsy procedure, there is no further 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.

If a pathology report indicates that further treatment is required, this will take place as per standard of care, but this is outside the scope of this investigation, and no data pertaining to further treatment will be used in the analysis for this investigation.

5.8.5 Monitoring Plan

Exact Imaging will assign personnel to the Study Monitor role for the investigation, and agrees to 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 sponsor,

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 sponsor,
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 sponsor,
j) findings of non-compliance or required modifications shall be reviewed with the investigator and disclosed in a written monitoring report to the sponsor.

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 the description of Exact Imaging's role as the Study Monitor for the investigation, Exact Imaging will ensure the quality of data related to the investigation by:

- on-site visits to Urology San Antonio at the beginning and end of the study
- 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
- 100% verification of all data

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

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

1. Review issues with investigators
    a. Study Monitor will discuss and investigate any performance issues and device deficiencies and resolved as required. These issues will be documented and signed by the Study Monitor, 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

2. Review subject enrolment

3. 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 one image saved on the system to correspond to each biopsy core.

d. Verify data. Compare images stored on ultrasound system with CRF data and pathology report

4. Copy and collect image data

5. 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.

For cases in which the Study Monitor observes biopsy procedures during a site visit, the Study Monitor 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 to be used in this investigation is designed to collect information about the location of the prostate where biopsy samples were taken, to provide a summary of findings from the pathology report entered locally, along with other notes from investigators.

Source data will be recorded on case report forms (CRFs) as follows:

- For each of the 12 systematic biopsy samples, investigators will indicate the PRI-MUS score for micro-US. (For every biopsy sample, an image of the biopsy location will be saved on ExactVu as well.)
- For each additional targeted biopsy sample, investigator will indicate the location and the PRI-MUS score for micro-US. (For every biopsy sample, an image of the biopsy location will be saved on ExactVu.)
- Pathology report will be entered on the CRF and a copy attached to the CRF. This is checked for accuracy by the Principal Investigator.
- mpMRI report will be entered on the CRF and a copy attached to the CRF. This is checked for accuracy by the Principal Investigator.

Note that the PRI-MUS protocol used here is derived from Ghai et al.[7]. This protocol for assessing risk in the micro-US images is investigational and has not been evaluated by the FDA.

Along with the data accuracy checks listed above, Exact Imaging will also check data prior to and during analysis as follows:

- Check pathology reports against what is entered on the CRF
- Logic checks on data, and follow-up on unusual data. (For example, if there is a case in which biopsy samples from targeted needles don't indicate cancer and samples from systematic needles do show cancer, an investigation would follow.)

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

The case report form to be used in this investigation 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 to maintain the privacy of the subject in the throughout the investigation. The Study Coordinator will make a subject's personal information available to the Study Monitor appointed by Exact Imaging, should it be required for monitoring, auditing or inspection by Western IRB if applicable.

It is the responsibility of the Study Coordinator (or designate) 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 Urology San Antonio 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
Urology San Antonio	On CRFs, on the ultrasound system, and on pathology records, subjects will be identified alphanumerically and sequentially, using USA-EV-0001, USA-EV-0002, etc.

5.9 Statistical considerations

5.9.1 Statistical design, method and analytical procedures

Case data will be analyzed by an independent third-party biostatistician using a statistical modeling software tool (PASS or MATLAB).

The primary endpoint is the relative detection rate (sensitivity) between mpMRI and micro-ultrasound for significant prostate cancer at a subject level. Power is based on the sensitivity of the test. Prevalence is assumed to be 60%.
H0: Sensitivity of micro-ultrasound/Sensitivity of mpMRI $\leq \delta = 0.76$
H1: Sensitivity of micro-ultrasound/Sensitivity of mpMRI $> \delta = 0.76$
where δ was based on results of comparing mpMRI to TRUS as noted below.
Specificity will be similarly tested. That is:
H0: Specificity of micro-ultrasound/ Specificity of mpMRI $\leq \delta = 0.67$
H1: Specificity of micro-ultrasound/ Specificity of mpMRI $> \delta = 0.67$
These analyses will be conducted at the subject level.

Non-inferiority Margin, δ
In the PROMIS study[11], the most recent confirmatory study of mpMRI to TRUS, mpMRI showed improvement in sensitivity of MP-MRI to TRUS from 0.93 to 0.48, respectively, with a test ratio of 0.52 (95% CI: 0.45-0.60) using McNemar's test. In order to preserve the effect of mpMRI versus TRUS as seen in this study, the non-inferiority margin for the test ratio of 0.76 (24%) was chosen as being equal to 50% of the effect from the point estimate of 0.52 to a ratio of unity (equal sensitivity). Then, the lower bound of the test ratio must not exceed 0.76 in order for non-inferiority to be declared in the current trial, thus preserving at least 50% of the effect of mpMRI versus TRUS. McNemar's test will be used to establish the (1-α) confidence interval for the test ratio.

Specificity from the same study was lower on mpMRI than TRUS with a test ratio of 2.34 (2.08–2.68). In the prostate biopsy procedure, since sampling is required regardless of imaging outcome (systematic sampling), specificity is less important. Still, we would like to preserve a reasonable specificity similar to mpMRI, therefore we select a non-inferiority margin of 0.67, or not more than 50% worse than the existing difference between mpMRI and TRUS (2.34*1.5 ratio to TRUS, 1/1.5=0.67 ratio to mpMRI).

Details of the design are presented in section 5.8.1.

5.9.2 Sample size

The trial will include 120 subjects. 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 micro ultrasound sensitivity of 0.85 and mpMRI performs at an expected 0.90 sensitivity, then 120 subjects would be required to provide 80% power to reject the null hypothesis, assuming 80% agreement between the methods.

PASS and 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 regardless of the assigned imaging modality.

5.9.5 Pass/fail criteria

The primary outcome of the study will fail if micro-ultrasound targeted biopsy fails to identify cancer in significantly more subjects than mpMRI targeted biopsy. This will be quantified by testing against the lower one-sided 95% confidence interval bound of the ratio of the two sensitivities, which must not be less than 76%.

5.9.6 Provision for an interim analysis

There are no plans for interim analysis during this clinical trial.

5.9.6 Criteria for the termination of the clinical investigation

There are no plans to stop the investigation early due to either early success or early futility.

The investigation will be terminated if Exact Imaging withdraws financial support for this study. In this case, Exact Imaging shall promptly inform the Principal Investigator of the termination or suspension and the reason(s) for this.

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 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

All analyses will be conducted on all enrolled and completed subjects. These analyses will also be repeated on the "As Intended" population, which includes only subjects for which there were no major protocol deviations.

A low risk sub-population is pre-specified for analysis. This population includes men meeting all of the following criteria:

1. PSA < 20ng/ml
2. PSAD < 0.15 ng/ml/cc
3. Negative DRE

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

This will allow data to be collected about the number of patients that withdrew from the investigation prior to the biopsy 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 section is not applicable to this investigation.

5.10 Data Management

Data will be stored on CRFs, and manually transferred to an analysis tool (MATLAB by Mathworks Inc.) by Exact Imaging personnel.

No subject-identifiable information will be transferred to MATLAB. 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 on a daily basis in accordance with Exact Imaging's standard operating procedures.

5.10.1 Data review

Source data will be verified during on-site visits by the Study Monitor, as described in section 5.8.5.1.

5.10.2 Data verification and validation

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

Source data will be verified during on-site visits by the Study Monitor, as described in section 5.8.5.1.

This data will be collected by the Study Coordinator or Study Monitor, 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 pathology reports
- data on CRFs and on images stored on ExactVu
- images stored on ExactVu and data on pathology reports

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 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 Western 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 Western 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 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. Western 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, Western IRB will be notified.

5.13 Device Accountability

ExactVu shall be used in the investigation according to the procedures documented in the CIP and referenced documents. The ExactVu instrument to be used is specified in section 5.4.1, and is currently leased by Urology San Antonio.

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 of FDA for conducting clinical investigations.

The investigation will not begin until the required approval is obtained from Western IRB.

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.

The Informed Consent form also includes an Addendum, using which a study subject may optionally give Exact Imaging permission to view images from previous prostate ultrasound or MRI examinations (if available). A subject may participate in the investigation without giving this permission.

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, Western IRB and Urology San Antonio 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 Western IRB as required within the required timeframe, and in the required format.

5.16.1.2 Adverse event report format

Reports must follow the Western IRB guidelines, and use the required reporting form. The required reporting form is the Promptly Reportable Information Form on Western IRB website: http://www.wirb.com/Pages/DownloadForms.aspx

5.16.1.3 Urology San Antonio Contacts

Urology San Antonio contacts are as follows:

- Study team during business hours Manuel Hernandez, Director of Research – (210) 731-2050
- Doctor on call after business hours David R. Talley, M.D. (210) 731-2050
- Western IRB: (800) 562-4789

5.16.2 Device deficiency reporting process

If a device deficiency does not require immediate resolution, it will be discussed between the principal investigator and the Study Monitor 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 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. Western 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 arrange for the return of ExactVu and related equipment and will collect case report form data for consideration towards future clinical investigations. Western IRB shall be informed promptly and provided with the reason(s) for the termination.

5.19 Publication policy

Exact Imaging permits 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.

No subject will be identifiable in any published results.

5.20 Critical Literature Review

(Literature reviewed June 26 2018)

Introduction

The current standard of care for detection and monitoring of prostate cancer is the transrectal ultrasound-guided biopsy (TRUS)[12]. This procedure is typically performed with a standard low-resolution ultrasound system (LR-TRUS), which does not reliably image cancerous lesions within the prostate. 62% of the time, no abnormalities are found using LR-TRUS imaging even in men with biopsy-confirmed prostate cancer[3]. This large percentage of lesions which are not visible during traditional LR-TRUS procedures require most protocols to use the modality only to visualize the prostate and guide systematic 12-core biopsies, although biopsies are targeted when a lesion is visible. Current research suggests that a large number of cancers are missed due to this mostly non-targeted, systematic approach[13,14]. Improving visualization of cancerous lesions during biopsy would improve detection rates, reduce the need for repeat biopsy, and potentially allow active surveillance protocols to follow tumors visually, rather than with periodic biopsy.

Ultra-high resolution TRUS (micro-US) utilizes higher frequencies (21MHz) than LR-TRUS in order to improve the resolution of prostate images. This has been demonstrated to improve sensitivity to detect cancer during the biopsy procedure[1–4,7,8]. A recent study by our group demonstrated an improvement over LR-TRUS in the ability to image cancerous foci, particularly for higher grade tumors[3]. These results have been supported by additional work in a screening population, leading to the development of the PRI-MUS risk identification protocol[7]. This study will attempt to further these results by providing a blinded comparison of micro-US and mpMRI in men undergoing prostate biopsy. The ability to visualize the cancerous foci in these subjects would be of significant value to increase confidence in the event of a negative biopsy result and help guide selection of therapy in the event of insignificant or localized disease.

Methodology

General

The PubMed/Medline and Google Scholar databases will be used to identify relevant literature. Further literature will be identified from the references in these studies. Search terms will include:

Prostate Cancer, Clinically Significant, Epstein Criteria, Confirmatory Biopsy, Serial Biospy, Active Surveillance Biopsy, Neoplasm Grading, Adenocarcinoma/Classification, Prostatic Neoplasms/Classification, High Grade, Ultra High Resolution Ultrasound, High Frequency Ultrasound, High Resolution Ultrasound

Objective

This review will attempt to cover the pre-clinical and clinical support for further clinical study of the micro-US technique, as well as provide justification for study enrollment numbers. Study risks will also be discussed.

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

Device description

The micro-US device is the next generation of the one used during our group's previous study[2]. This new commercial version of the device has received marketing clearance in the United States from the FDA. The intended use of the device is to visualize the prostate in order to guide the TRUS biopsy. Other than the higher resolution, this is equivalent to a standard ultrasound device of the type commonly used to guide TRUS procedures and that represents the current standard of care.

The micro-US device provides a high-resolution image of the prostate, with a field of view that includes the entire prostate (subject to the size constraints in the screening exclusion criteria). More detail on the device itself and safety tests conducted in order to comply with IEC medical device standards is identified in this CIP.

Analysis of selected literature

There is significant literature demonstrating the use of high-frequency ultrasound for in vivo visualization of both healthy and cancerous tissue. Much of this literature is in the form of pre-clinical animal models[5], but the device was also used in a previous clinical trial at Johns Hopkins University[2]. This previous clinical trial from our group demonstrated improved visualization of cancerous foci by micro-US compared to LR-TRUS with superiority in both sensitivity and specificity when compared to pathological findings on radical prostatectomy[2]. This work has been published in a highly regarded international peer-reviewed journal. Another clinical trial has recently completed, run by our group (WIRB Protocol 20131849). Data from the first half of this trial was used to develop the PRI-MUS risk identification protocol[7]. This large, randomized clinical trial was designed to demonstrate improved cancer detection rates in men without a known history of prostate cancer (a screening population of 2000 men). The results of this trial are now available, and suggest significantly improved sensitivity over conventional ultrasound.[4] Safety information, including from this previous trial, is reported elsewhere in this CIP. The proposed study aims to compare the micro-US technology with another imaging technology that has been demonstrated to provide high sensitivity to prostate cancer.

Enrollment numbers for the micro-US study were calculated by the sponsor based on the following review of the literature. Factors affecting required enrollment include the ability of mpMRI and micro-US to target prostate cancer, and the number of subjects with cancer in this population.

Two recent studies were found that investigated rates of successfully targeting prostate cancer with greyscale LR-TRUS using biopsy as the reference standard, all other studies were pre-1990 and are considered less relevant due to substantial improvements in imaging technology. These studies vary considerably in the aggressiveness of their targeting, with Barish et al.[15] demonstrating a sensitivity of 40% (specificity 80%, N=544) and Nelson et al.[16] a sensitivity of only 26% (specificity 89%, N=137). Weighted average sensitivity and specificity are 37.2% and 81.8% respectively. This sensitivity value is very close to that found during our pilot study[3] against the more accurate radical prostatectomy (RP) reference (37.7%), however the specificity value in that study was much lower (65.4%). This may be due to the low N=25 of that study, or the greater accuracy of the RP reference. If micro-US provides a more accurate biopsy reference (closer to RP), we may expect a specificity between 81.8% and 65.4%. The PROMIS trial[17] did not test targeted biopsy on LR-TRUS, but did report the sensitivity of systematic biopsy using LR-

TRUS to detect prostate cancer. This value is reported as 48%, which demonstrates the value of the additional systematic biopsy cores due to the poor sensitivity of targeted only sampling using this modality. This higher value will be used to define the non-inferiority threshold, in order to be as rigorous as possible.

The PROMIS trial[17,18] provides the highest quality evidence of prevalence in this population, using template mapping biopsy to demonstrate clinically significant cancer in 308/572 subjects (54%). This is a reasonable value given other meta-analyses demonstrating detection rates from 24%-87% in the literature[19–21].

Sensitivity of mpMRI has varied widely in the literature as demonstrated by numerous meta-analyses[19,21,22], showing detection rates ranging from 24%-87%. The PROMIS trial[17] found a sensitivity of 88% for predicting clinically significant prostate cancer, but did not perform targeted biopsy. Therefore, this value could be seen as a maximum possible when perfect targeting and histopathology is assumed. In cases with targeted biopsy, such as the PRECISION trial[23], mpMRI detected significant cancer in 38% of the arm vs. 26% in the systematic biopsy arm. Assuming a similar 54% incidence this amounts to sensitivities of 70% and 48% respectively which compare well with our own feasibility cohorts demonstrating sensitivities of 56-85% for mpMRI[1,2,8] and previously discussed sensitivity data for systematic biopsy.

Sensitivity data on micro-US is available from 2 cohort studies and 1 randomized trial. These three datasets suggest sensitivities of 83% (N=60)[2], 98% (N=79)[1], and 61% (N=286)[4] for a weighted average of 71%. While this average is biased towards the earlier data from the randomized trial, this study was conducted on an early version of the device with little training on the PRI-MUS risk identification protocol, therefore we expect this to underestimate the true sensitivity of the micro-US modality.

Given an incidence of approximately 50% with sensitivities of mpMRI and Micro-US of approximately 66% and 75% respectively, 108 subjects are required to provide 80% confidence of achieving non-inferiority within 20%. This non-inferiority bound was chosen to maintain at least 50% of the benefit of mpMRI over conventional systematic biopsy providing a sensitivity of approximately 48%.

Evaluation of hazards, risks and safety measures
The risks associated with the TRUS biopsy procedure are well captured in the literature, and represent the normal standard-of-care for subjects with the inclusion criteria of this study[6,24–27]. Data from our previous study, and preliminary data from our ongoing clinical trial, suggest that these risks are not significantly altered due to the micro-US probe[3]. Risk minimization will follow the same standard-of-care procedures as LR-TRUS, including antibiotic prophylaxis and management of bleeding risk[6,24–27].
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 visualizing cancer in TRUS-guided biopsy procedures. A multiple-imaging case series allows for direct comparison between modalities and maintains standard-of-care for all patients with little or no additional risk. 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
    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 Western IRB's approval/favourable opinion is obtained and documented, and that appropriate provisions are made to meet any conditions imposed by Western IRB
g. ensure that any modification(s) required by Western IRB or regulatory authority are made and documented by the Principal Investigator and have gained the approval/favourable opinion of the Western 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 Western 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 Western 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 Western 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