Study Protocol

A proof-of-technology, pilot, single-site, open-label, prospective clinical study to investigate the feasibility and performance of PROVIZ – a radiomics-based machine learning software, to support targeting of prostate biopsies on magnetic resonance images in biopsy-naive patients.

This document represents a direct extraction of pertinent sections from the approved Clinical Investigation Plan (CIP) Version 1.5, dated 22nd January 2024, tailored to outline the study protocol.

1.1.1 List of abbreviations:

Abbreviation	Term
ADC	Apparent diffusion coefficient maps
ADE	Adverse device effect
AE	Adverse event
AI	Artificial intelligence
ASADE	Anticipated serious adverse device effect
AUC	Area under the receiver operating characteristic curve
bpMRI	bi-parametric MRI
CAD	Computer-aided detection and diagnosis
CIP	Clinical investigation plan
CRF	Case report form
csPCa	Clinically significant prostate cancer
DD	Device deficiency
DRE	Digital rectal examination
DWI	Diffusion-weighted imaging
eCRF	Electronic Case report form
EU	European union
FROC	Free-response receiver operating characteristic curve
GUI	Graphical user interface
Hemit	Central Norway regional health IT
IB	Investigator's brochure
ICD	Informed consent document
ID	Identity document
ISO	International organization for standardization
mpMRI	multi-parametric MRI
MRI	Magnetic resonance imaging
NTNU	Norwegian university of science and technology
PACS	Picture archiving and communication system
PI	Principal investigator
PI-RADS	Prostate imaging-reporting and data system
PSA	Prostate-specific antigen
REC	Regional committee for medical and healthcare research ethics
SADE	Serious adverse device effect
SAE	Serious adverse event
SaMD	Software as a medical device
SIL	Subject identification log
SLV	The Norwegian medicines agency
SOP	Standard operating procedure
T2W	T2-weighted imaging
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious Adverse device effect

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6.4 Procedures

6.4.1 Clinical investigation procedure

The clinical investigation procedure is summarized in Figure 6.4.1 and the decision to send patients for biopsy sampling summarized in Figure 6.4.2.

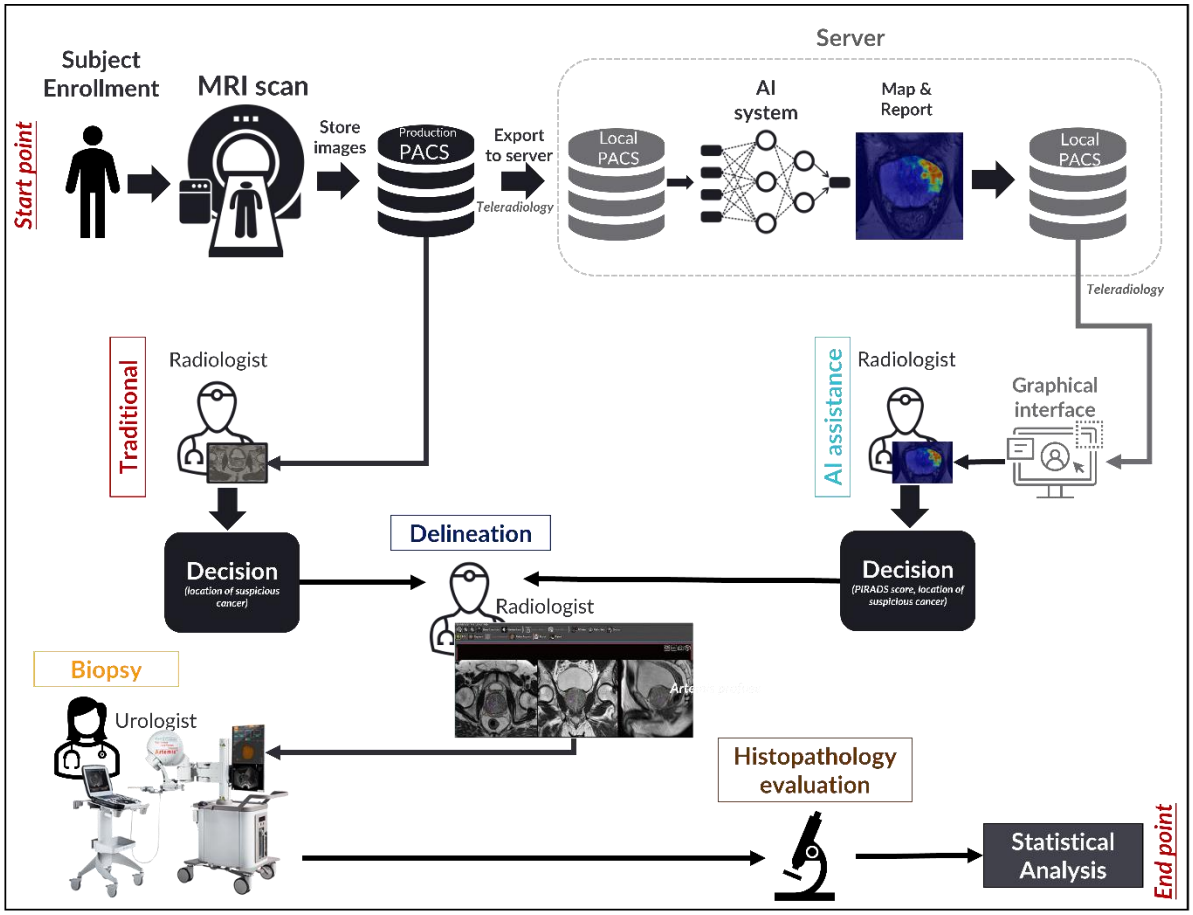

Figure 6.4.1: Summary of the clinical investigation workflow.

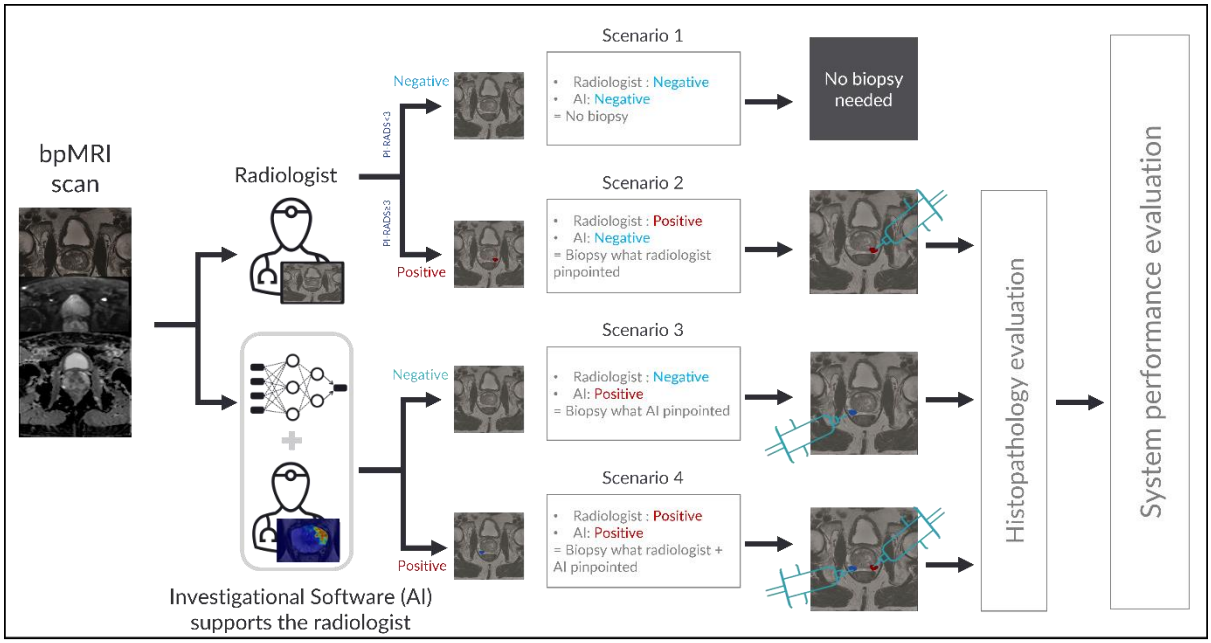

Figure 6.4.2: Simplified explanation on how lesions are selected for biopsy during the prospective study.

The patient meets for an invited MRI scan due to a suspected prostate cancer according to current clinical practice. A research coordinator checks to see if the patient meets the inclusion criteria for the investigation. This is done by asking the patient and checking the patient records. If the patient meets the criteria, then he is eligible for enrollment. He is then given an informed consent to participate that explains the purpose of the study, the risks and benefits, and the participant's rights in layman's terms. Oral and written information will be given to the patient prior to scanning, and any questions will be answered. Patients accepting to take part will sign the informed consent after the scanning.

The clinical investigation step by step as follows:

1. Patient scanned using MRI with bpMRI protocol.
2. The patient scan is stored in the production PACS (i.e., the hospital PACS) system.
3. The images will be deidentified and the patient will get a pseudonym, before they sent to the local PACS (i.e., the study server PACS). All the of the sensitive, identifiable, and locatable information by means of a standard identification mechanism within the metadata for the patients and the physicians will be anonymized.

4. A password-protected Subject Identification Log (SIL) linking subject names to newly assigned IDs will be created and updated for each newly enrolled subject. The spreadsheet is stored in the hospital system and the password is only accessible to authorized individuals.
5. The images will be sent to the local PACS on the sever via teleradiology.
6. The radiologist will open the patient scan using the production PACS, as usual, check the images, and identify the suspicious areas, which need to be biopsied, according to PI-RADS.
7. The radiologist will open the GUI desktop application from his/her workstation and check the software outputs (i.e., tumor probability map, the detection map, and gland segmentation). Here the pseudonym will be used from the SIL to enquire the subject in the local PACS.
8. The radiologist compares his/her findings with the results of the investigational software. If there are areas detected by the software (detection map) that were not detected by the radiologist, the radiologist selects these areas (up to 3 areas).
9. The radiologist will fill a report in the eCRF to be used by researchers only, flagging the detected areas for biopsy sampling into:
    a. Defined solely by the radiologist, with PI-RADS score + location.
    b. Overlap between the radiologist and the investigational software, with PI-RADS score + location.
    c. Defined solely by the investigational software, with location.

    The location should be according to the areas identified by PI-RADS (Figure 6.4.3). Table 6.4.1 gives an example on the report.

Table 6.4.1: Example of radiological report of findings, for research purposes only.

Pseudonym		***POT0001***		
Finding number	**Human**	**Investigational software**	**Finding Location**	**PI-RADS score**
1	x		Mid-PZpm-R	3
2	x		Apex-PZa-L	4
3	x	x	Base-PZpl-R	4
4		x	Mid-PZa-L	N/A

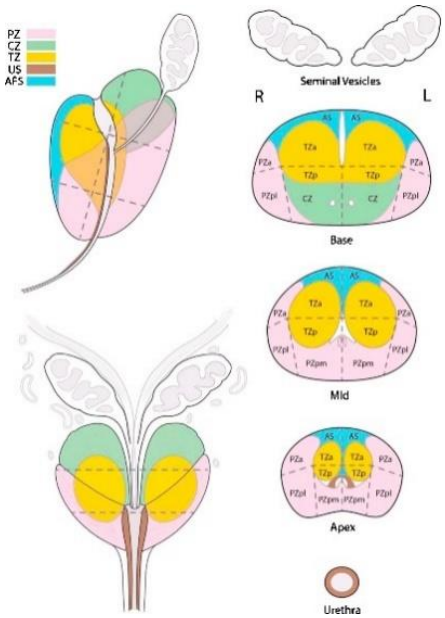

Figure 6.4.3: The prostate regions according to PI-RADS.

10. The radiologist fills out the report as usual without identifying whether a finding is identified by the investigational software or human, keeping the lesion number. The radiologist will add a sentence to his report indicating that some of these lesions may have been identified by investigational software.

11. The radiologist then opens Eigen Artemis Profuse software (Eigen Health, CL, USA) to delineate the prostate and suspicious lesions as usual. The radiologist semi-automatically delineates and adjusts the entire prostate after reviewing the automatic segmentation on the GUI screen. This is followed by delineation of the suspicious findings by the radiologist and the AI (up to 3 solely AI findings). Note that radiologists begin delineation in order (i.e., lesion 1, then 2, then 3, then 4, as indicated in the report in order).
12. The radiologist will export the delineations file to the Eigen ARTEMIS - Prostate Fusion Biopsy System (Eigen Health, CL, USA).
13. The urologist will review the radiologist's report and unless the patient has contraindications to prostate biopsy (due to comorbidity or remaining life expectancy) the patient will be registered for biopsy sampling procedure.
14. When the patient arrives for the biopsy, he is prepared as usual.
15. Prior to biopsy, the operating room nurse will import the radiologist's segmentations into the Eigen ARTEMIS - Prostate Fusion Biopsy System (Eigen Health, CL, USA).
16. The urologist will perform an ultrasound scan for fusion with the MRI scan.
17. The urologist will then obtain biopsies according to the standard clinical procedure. This includes targeting the delineated suspicious areas at least once. In some cases, the urologist may perform a systematic biopsy in addition to the targeted biopsy. The urologist will ask the nurse to place each biopsied specimen in a plastic tube immediately after collection and to immediately label the tube with Lesion 1, 2, 3 ... etc. (corresponding to the lesion number assigned by the radiologist for the targeted biopsies) in addition to labelling the biopsy location according to PI-RADS (Figure 6.4.3).
18. The tubes are sent to pathology department for histopathological evaluation. Each lesion is evaluated separately. Some suspicious areas may have more than one biopsy taken from them. Then they are pooled and evaluated together to determine the overall Gleason score for each lesion separately.
19. The data will be collected by the researchers, once every week, where the patient pseudonym (e.g., POT0001) will be used to name folders and deidentify scans upon exporting. The subject's scan images are pseudonymized and exported to an encrypted external hard drive and then uploaded to the lab at HUNT cloud. The graphical report of the biopsy procedure might be exported from the ARTEMIS

system to an encrypted external hard drive and then uploaded to the laboratory at HUNT cloud. The radiologist's report on the patient is exported to the Digital Life lab at HUNT cloud. The patient's clinical information is collected and exported to the lab at HUNT cloud. The lesion-based histopathology assessment report is exported to the lab at HUNT cloud.

20. The data collected will finally be used for analyses according to primary and secondary objectives of the study.

Overall, the deviation from normal clinical practice is very small. Deviations mainly relate to subject enrollment, the inclusion of test software in image analysis, and the storage and export of data for research. Specifically, the deviation is in steps 3, 5, 7, 8, 9, 19, and 20.

Steps 3, 4, and 5 will be performed by HEMIT; steps 7, 8, and 9 will be performed by the radiologist; and steps 4, 19, and 20 will be performed by the sponsor's representatives (research coordinators), see Section 6.4.2.

Additional activities to the above procedure include user reporting of safety-related concerns or adverse events, or software-related bugs or errors to the PI and communication between the clinic and the PI to determine if it is necessary to suspend or terminate the study early. In addition, software users will be trained in the proper use of the software prior to the start of the investigation.

14. 5 Procedures for recording and reporting Adverse Events and Device Deficiencies

All adverse events, effects, device deficiencies, and related information will be recorded in detail in the medical records and the eCRF by the investigator or one of his/her delegate. The investigator will report all of these to the sponsor as it is specified in Table 14.4.1. The Sponsor will report all reportable events to the SLV in accordance with the SLV reporting procedure within the timeframes specified in Section 14.4.