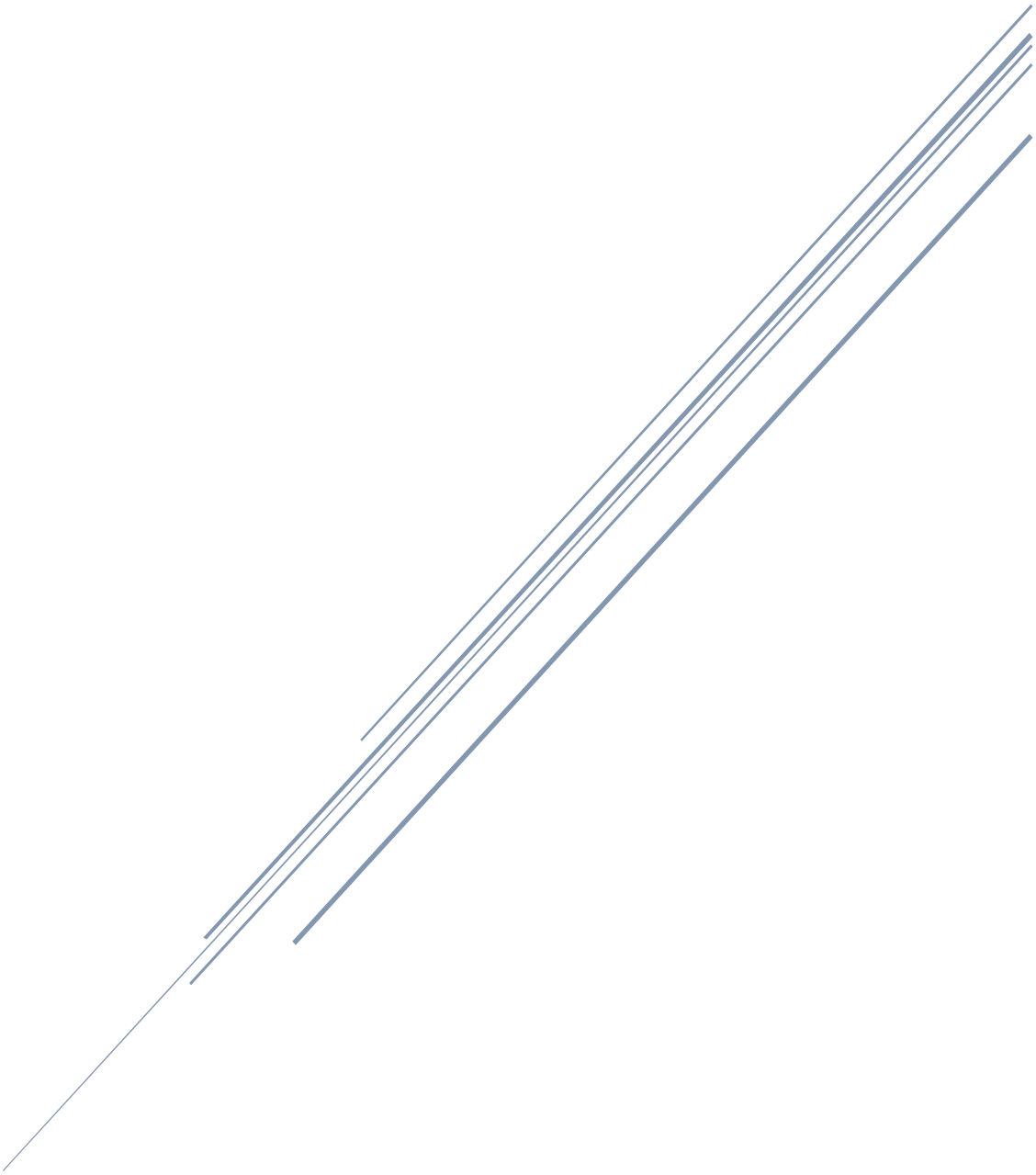
A Proof of Concept Study Evaluating the Role of Emerging Ultrasound Technologies in the Assessment and Monitoring of Localised Prostate Cancer in Men on an Active Surveillance Programme

Study Protocol: Evaluating the Role of Ultrasound in Prostate Cancer (ERUP)

6th December 2021



Hull University Teaching Hospitals NHS Trust

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Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Full title of the research:

A proof of concept study evaluating the role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme.

Short title for this project:

Evaluating the role of ultrasound in prostate cancer

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Abstract

Research plan, study design and protocol

Summary of the study:

Active surveillance (AS) is becoming an increasingly common treatment option for men who have been diagnosed with localised low-grade prostate cancer (PCa). Low-grade disease is commonly noted by clinicians to be clinically insignificant cancer but remains a psychological burden to many men in this cohort. There is consensus that regular review is required for men on AS so that early treatment can be undertaken if there is disease progression, and to support men living with a cancer diagnosis. Some AS protocols, including NICE, advocate the use of MRI as a regular part of the monitoring pathway. Unfortunately, access to MRI for AS, within the current health care environment in the UK, is limited due to increasing demand for primary diagnostic examinations, particularly in the post Covid-19 recovery phase. Emerging technologies in ultrasound imaging may, however, add another diagnostic tool to monitor disease for patients on AS. This proof of concept study is to evaluate whether new multi-parametric ultrasound techniques can safely reduce the number of MRIs required for effective AS.

Men being investigated for PCa will be invited to undergo an ultrasound examination of their prostate, via the rectum, in addition to the diagnostic MRI undertaken as part of normal care. The findings of the ultrasound will be directly compared with the MRI and any subsequent biopsy samples taken as part of routine care. Those who then progress onto AS will be invited to undergo regular rectal prostate ultrasound examinations. These will be compared with previous imaging for signs of change.

This study will also evaluate the changing role of practitioners who will be using new technologies and making decisions about disease progression. The ability to implement new techniques will be assessed. All imaging will be undertaken at Castle Hill Hospital over a 24-month period from commencement of the study.

Contents

Research Plan

1.1 Purpose and design

Across the UK prostate cancer is the most common cancer in men. Developments in magnetic resonance imaging (MRI), and the implementation of a targeted biopsy regime, have resulted in a considerable improvement in the detection of prostate cancer. The advent of robotic prostatectomy, and improvements in radiotherapy, have both lessened the post-treatment side effects but no treatment is without significant risk of complications.

1.1.1 Clinical context:

Prostate cancer can be present as an indolent low-grade cellular change to the tissue but with very little risk of this progressing to a metastatic life threatening disease. Despite the improved diagnostic capabilities, there remain a significant proportion of men in whom low-grade cancer is detected and consequent treatment options may present a higher risk to quality of life than the presence of the localised disease. NICE CG 131 (2019) recommends men are offered active surveillance (AS) or watchful waiting (WW) as an option for low-risk localised prostate cancer and for whom radical prostatectomy or radical radiotherapy is suitable should advancing disease be detected. Both AS and WW involve proactively monitoring the patient for signs of disease progression rather than undertaking treatment immediately. Patients on an AS pathway are deemed suitable for intervention and curative treatment should there be signs of disease progression; patients on a WW pathway usually have comorbidities that preclude curative treatment but they may benefit from palliative care if there is evidence of future progression. The Prostate Testing for Cancer and Treatment (ProtecT) (Hamdy et al. 2016) trial was established to gain a better understanding of the effectiveness of treatments, including AS, for prostate cancer. ProtecT (Hamdy et al. 2016) concluded that, at a median of 10 years, prostate cancer specific mortality was low regardless of the treatment assigned and that adopting an AS approach is reasonable to avoid life limiting side effects (Da Silva et al. 2017, Klotz et al. 2015).

However, despite the findings of the ProtecT trial (Hamdy et al. 2016) and the NICE guidance 131 (NICE 2019) there is currently no standard approach to AS due to the inequalities in capacity and availability of services in the NHS. It is, however, agreed that men on AS require regular tests which should include a combination of the following:

- Prostate Specific Antigen (PSA)
- digital rectal examinations (DRE)

- MRI scans
- prostate biopsies – either transrectal random or transperineal template biopsy

The improvements in MRI imaging and reporting indicate that regular scans would add valuable information for patients under AS but capacity is significantly hindering this as an available application. An overview of the current clinical pathway for patients in the local region is provided as appendix 1. This highlights the very real impact that capacity issues in MRI has on patient diagnostic pathways.

1.1.2 Technological improvements

However, emerging technologies in ultrasound imaging, which is less hindered by capacity issues within the UK and is utilised, to a degree, in current standard care, may add another diagnostic tool to monitor disease for patients on AS. A multi-parametric ultrasound assessment may provide the crucial diagnostic features that enables ultrasound imaging to be used to monitor disease. A multi-parametric assessment will include standard frequency ultrasound, Doppler ultrasound and high frequency ultrasound imaging. High frequency ultrasound (micro-US) increases the detail of structures imaged, compared to standard trans-rectal ultrasound, and has been demonstrated to be a promising new modality for targeted prostate assessment compared to MRI (Maffei et al. 2019). A recent paper by Matheson et al. (2019) has demonstrated that most men on AS cope well psychologically but the paper is limited in its exploration of what alternative intervention could be made to improve well-being within a AS programme. A crucial question remains as to whether the use of additional imaging and health care intervention could improve patient outcomes.

1.1.3 Implementing change

Traditionally, radiologists or urologists have performed the diagnostic transrectal prostate biopsy procedures within the cancer pathway. In more recent years, skill mix has developed and there is an increasing number of sonographers undertaking these examinations enabling medical capacity to be released. Within the Hull University Teaching Hospitals NHS Trust, the vast majority of prostate biopsies are undertaken by sonographers. Sonographers are trained and qualified to interpret ultrasound imaging. They provide diagnostic reports as part of routine practice. The limitations of traditional US technology used to guide transrectal prostate biopsy precluded any diagnostic assessment during the biopsy procedures; US is used purely to guide where samples will be taken.

1.1.4 Skill mix

The advent of multi-parametric ultrasound may enable a diagnostic assessment of the prostate, both at the initial biopsy and during AS. This will be an additional skill the sonographer will be required to develop. The benefits of skill mix have been documented by various authors, most recently Field and Snaith (2013). However, the impact of role development on sonographers and their radiologist colleagues, which includes changes to roles, responsibilities and accountabilities, has not been previously investigated in any depth. A workforce review by Parker and Harrison (2015) identified that appropriate training in ultrasound is key to providing a safe diagnostic and interventional ultrasound service but what constitutes appropriate training is less well defined.

1.1.5 Normalisation Process Theory (NPT)

Despite the publication of a defined framework for the development and evaluation of research, there remain substantial problems in the design and conduct of studies introducing complex interventions and their subsequent implementation (Finch et al. 2018). The understanding of an implementation processes is key to ensuring that proposed changes to techniques, technologies or interventions are both implemented and sustained in practice; desired outcomes of a 'successful' implementation do include the experiences of those providing the service. If a new technology provides good diagnostic results but is cumbersome and complex to use, it is unlikely to be implemented into routine healthcare practice. A recognised gap exists between developing new treatments and knowledge, and implementing these in practice for the patient who may benefit (De Brún et al. 2016, May, Johnson and Finch 2016). An understanding of the ability to implement the proposed new complex ultrasound techniques in real-life clinical practice will be explored within this proof of concept study. Normalisation process theory (NPT) is the theoretical approach being utilised in this study. NPT is a theory which described the collective work that stakeholders need to engage in to implement interventions in the real world of everyday clinical practice. NPT has 4 components that practitioners need to adopt in order to embed a new process or technology into routine practice. The 4 components: Coherence, Cognitive Participation, Collective Action, and Reflexive Monitoring. These will be explored further in the staff focussed third phase of the study.

1.2 Study Aim

This aim of this proof of concept study is to evaluate if emerging ultrasound technologies can provide reliable and reproducible imaging that can be used to assess the prostate gland in men with known localised prostate cancer and who are being managed with active surveillance.

The impact of additional skill mix for health care practitioners within diagnostic imaging, in the field of prostate cancer assessment and monitoring, will be investigated as a secondary objective of this study. As with many research studies, data is collected in a strict and controlled environment which may not readily translate into a real life clinical setting. The feasibility for implementing changes to the imaging pathways in active surveillance will also be evaluated with the clinical team delivering the current and future service.

1.3 Primary and secondary objectives

1.3.1 Primary objective

The primary objective of the study is to evaluate if emerging multi-parametric ultrasound technologies can provide a viable tool to be used in the active surveillance of men with known localised prostate cancer.

1.3.2 Secondary objectives

Secondary objectives of this study are:

- to evaluate the diagnostic parameters of diagnostic ultrasound that can be utilised to assess disease within the prostate gland.
- To evaluate the diagnostic parameters of diagnostic ultrasound that can be utilised to assess disease progression within the prostate gland.
- To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland can be investigated.
- To determine if a suitable standardise imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.
- To gain a better understanding of how new ultrasound technology and techniques can be implemented and embedded into clinical practice.

1.4 Study phases

This study is being undertaken as a PhD research project but within the NHS care setting. The study will consist of four phases:

1.4.1 Phase 1:

In this initial phase, eligible men who have consented to participate will undergo a transrectal ultrasound examination with a standard ultrasound probe and, at the same attendance a transrectal ultrasound examination with a new and novel probe using 29MHz scanning frequency. The images obtained from this examination will be retrospectively compared with the MRI imaging that has been obtained as part of the standard care pathway. The images obtained will be reviewed by two

health care practitioners with experience in prostate imaging and the outcomes of these reviews compared to evaluate agreement levels.

1.4.2 Phase 2:

The second phase of the study will evaluate the use of multiparametric standard and micro ultrasound in the assessment of men who are on an AS or WW pathway. This phase the study will evaluate if there are any changes in the findings at repeat ultrasound examinations that can indicate disease progression. Eligible men, who have consented to participate, will again undergo a transrectal ultrasound examination with a standard ultrasound probe and, at the same attendance a transrectal ultrasound examination with a new and novel probe using 29MHz scanning frequency.

1.4.3 Phase 3:

The process and acceptability of implementing new interventions and technologies into everyday clinical practice is frequently overlooked following research trials. This third phase will explore the views of the health care practitioners, who have consented to participate, regarding the use and implementation of the proposed new technologies; skill mix between these professional groups will be required for successful long term practice. The participants will be recruited from differing professionals within the staff groups of Hull University Teaching Hospitals NHS Trust. An adapted survey tool, derived from normalisation process theory framework, will be used to better understand how and if the new, complex, multi-parametric ultrasound techniques can be implementation within the organisational setting of everyday routine practice. A baseline assessment of confidence in knowledge and skills related to prostate cancer evaluation using ultrasound will be made.

1.4.3.1 Staff training:

Participants in phase 3 will then be provided with training using specific multi-parametric US techniques and will regularly score multi-parametric US examinations. Participants' confidence in knowledge and skills, related to prostate cancer evaluation using US, and how they feel this can be implemented into regular patient care will be assessed, using the same adapted survey at baseline at 6 - 12 months' post implementation.

1.4.4 Phase 4:

A fourth phase of the study is planned. Once outcomes from the initial 3 phases of the study are known the lead researcher intends to organise a national meeting where results will be presented and discussion held between the research team and other centres providing a diagnostic prostate cancer service. The aim of this event is to disseminate results and to obtain a wider understanding of

its acceptance beyond local practice. Multi-parametric ultrasound is novel and there may be resistance to wider implementation. Opportunities and barriers will be explored at this phase 4 event.

The study phases will run concurrently and will be managed by the lead researcher.

1.5 Study design and methodology – Phase 1

1.5.1 Phase 1: Patient population

With consent, all eligible men will be invited to participate in the first phase of the study; appendix 1 outlies the current care pathway and the eligibility criteria utilised in this study. Multi-parametric US will be used to assess the prostate gland prior to the ultrasound guided diagnostic prostate biopsies which is performed as part of routine care. The multi-parametric US examination will be performed blinded to the pre-biopsy MRI undertaken as part of routine care. Multi-parametric US findings will be scored and subsequently correlated to MRI and any related histology findings which are recorded as part of routine care.

1.5.2 Eligibility criteria in clinical practice

MRI is offered to all men who meet the eligibility criteria of age ≤75, PSA ≤ 20 and life expectancy of ≥ 10 years. MRI is reported using the PI-RADS V2 criteria; a 5 point scale with 1 & 2 highly unlikely to have significant prostate cancer, 4 & 5 highly likely to have significant prostate cancer and PI-RADS 3 equivocal and further investigation warranted. The pathway in the Hull University Teaching Hospitals NHS Trust is that patients with PI-RADS score of 1 or 2 are not routinely offered biopsy due to the risk of biopsy complications being greater than the likelihood of prostate cancer. Men meeting these criteria will be invited to participate in phase 1 of the study and the multi-parametric US will be correlated with MRI only. A biopsy will not be performed. Any men from this cohort electing for AS will be invited to join phase 2.

1.5.3 Phase 1 recruitment

Participants for phase 1 of the study will be invited from the cohort of patients referred into Hull Teaching Hospitals with suspected prostate cancer and who meet the criteria for pre prostate biopsy MRI. Appendix 1 outlines the current clinical pathway and participants for the study will be invited from those who fulfil the criteria for pathway A of the local service.

1.5.4 Sample size – phase 1

As this is a proof of concept study testing the technology of ultrasound and with no previous comparable data little is known about the standard deviation and the distribution of US scores. This

makes determining a sample size based on means and variances difficult. Therefore, a sample size estimation is based on a representative proportional of the annual referral rate into this service. The sample size for phase 1 will be a minimum of 30 patients and a maximum of 60 patients. This represents 5% - 10% of the total patient population presenting with suspected prostate cancer and undergoing prostate biopsy in one calendar year. Given the small numbers within this cohort, all eligible participants will be invited to continue onto phase 2 of the study with maximum cohort of 30 being accepted.

1.5.5 Inclusion criteria for phase 1

The recruitment criteria and pathway for the clinical phases of the study are outlined in the flow charts, appendix 1 and appendix 2. These identify when the participants will be invited to participate, when consent will be obtained and the broad outline of the involvement in the study that participants can expect.

Men referred to urology within Hull University Teaching Hospitals NHS Trust with suspected, but undiagnosed, prostate cancer and:

- Are aged equal to 75 or less
- PSA equal to 20 or less
- Have had a clinical assessment and deemed to have a life expectancy of 10 years or more
- Are able to tolerate a rectal ultrasound examination
- Able to provide informed consent to the study
- Have had a multi-parametric MRI performed as part of routine care pathway
- MRI results will not preclude invitation for participation; men with PI-RADS 1 & 2, who would not be offered biopsy under routine care, are also included in the study. This phase 1 US imaging will be an addition examination for this cohort of patients. Consent for the addition imaging is required. Reference is made to the Phase 1 PIS (v2 03.11.21) and phase 1 ICF (v2 03.11.21).

1.5.6 Exclusion criteria for phase 1

- Patients accessing care in Hull University Teaching Hospitals NHS Trust but who are not suspected of having prostate cancer
- Men referred to urology but who do not meet the eligible criteria for MRI as part of the routine care pathway. This includes men who are over 75 and / or have a PSA over 20
- Men who meet eligibility criteria but in whom MRI has not been completed (due to lack of compliance, artefact, contraindications etc)
- Men who are eligible for inclusion but who cannot tolerate rectal ultrasound examinations.

- Men who are unable to consent to the study

1.5.7 Phase 1 recruitment process

Patients are seen in a specific prostate assessment clinic by a urology nurse specialist. A clinical history is taken and from there, referrals for both MRI and ultrasound guided prostate biopsy are made. At this appointment, all patients will be given an information leaflet for the study. The MRI is undertaken within 14 days of referral; the ultrasound guided prostate biopsy can only be performed following the MRI. The MRI can be distorted due to post biopsy haemorrhage in the prostate gland, and, more importantly, the MRI provides crucial information related to suspected areas of pathology in the gland which are targeted during the biopsy procedure. During the time from referral to MRI the patient will be contacted by the lead researcher and invited into the ultrasound study.

1.5.8 Ultrasound appointments – phase 1

A mutually convenient appointment will be made and confirmed with an appointment letter. The phase 1 recruitment pathway is provided in appendix 2. The patient will attend at the agreed date and time and a face to face consultation with the lead researcher will be undertaken to discuss the study and obtain written consent. The lead researcher will be blinded to the results of the MRI or previous studies at this time to minimise undue coercion into the study.

1.5.9 Image collection

Once written consent has been obtained, the patient will be shown to a private changing area, directly adjacent to the ultrasound examination room and asked to change into a hospital gown. The patient will be escorted into the scan room for the procedure to be undertaken. A chaperone will be present with consent of the patient, as per standard clinical practice. A randomly allocated sonographer who has consented to participate in the study will be introduced and verbal consent obtain for the procedure to commence.

1.5.10 Scan protocol

The patient will be positioned in a left sided-decubitus position or lithotomy position depending upon which is most comfortable for them. Once comfortable an ultrasound probe from a standard ultrasound machine with a scan frequency of 7.5MHz, and about the size of an adult male's index finger, is gently placed into the rectum and the prostate identified. The following images of the prostate will be obtained and saved onto the PACS system

During the ultrasound examination, the prostate gland will be scanned in a longitudinal and transverse plane from the apex to base, including seminal vesicles, and from right lateral border to

left lateral border. A standard imaging preset will be used and no changes to the scan frequency, or pre-processing software are to be made. The scan will be captured and stored as a video loop.

Systematic still images of the prostate will also be captured and stored. The systematic images acquired are:

1.5.10.1 Longitudinal plane:

Right lateral	Left lateral
Right mid	Left mid
Central/ Midline	

1.5.10.2 Transverse plane:

Seminal vesicles	Base
Mid gland	Apex

The prostate volume will be calculated using the following standard volume formula: height (cm) x width (cm) x length (cm) x 0.53 and documented in mL.

Colour flow Doppler imaging will be applied to evaluate the presence of any perfusion within the gland. With colour flow Doppler applied the same set of images will be stored.

The probe will be removed.

The examination will then be repeated using high frequency micro-ultrasound technology. Again, a standard imaging preset will be used and no changes to the scan frequency, or pre-processing software are to be made. This repeat examination will involve a second probe being inserted into the rectum, again about the size of a large male adult's index finger. Imaging of the prostate at 29MHz will be undertaken. Cine loops of the right and left lobes of the gland will be recorded. Five still images of the prostate will be captured at the midline, right mid gland, right lateral gland, left mid gland, and left lateral gland.

The probe will be removed. Both ultrasound examinations will take no more than a maximum of 10 minutes to complete (5 minutes each scan). Standard infection control procedures will be undertaken to clean ultrasound equipment, the examination couch and all peripherals.

The image collection for the study is complete and the patient will then proceed to undergo standard care dependent upon the findings of the MRI. The patient will be met by the sonographer

assigned to provide the consultation and biopsy as part of the standard care. Findings of the MRI will then be discussed with the patient and the patient's pathway will proceed as normal.

1.5.11 Data collection - Phase 1

Each participant will be given a unique study ID number. All images, cine loops and data for the study will be acquired and stored under this separate study ID. The data will be stored on the Hull Teaching Hospitals password protected picture archive and reporting system (PACS). A password protected database, stored in a password protected network drive of Hull Teaching Hospitals will hold the unique identifier number and will be used to record study data.

The lead researcher will randomly allocate a unique identifier number to two of the participating healthcare professionals. The reviewers will be randomly allocated to reduce bias as far as possible within a small team. Each reviewer will have their own unique identifier number known only to the lead researcher. The identity of the reviewers will be anonymised. The images and cine loops stored for the study will have no patient identifiable data on them. Appendix 4 outlines the image acquisition and review pathway for phase 1 of the study.

1.5.12 Data assessment

The set of images and cine loops will be reviewed, in retrospect, by the assigned reviewers. The images and cine loop will be reviewed via a PACS workstation with monitor quality, and viewing conditions, as similar as possible to the ultrasound monitors and scan rooms. The save images will be scored using a 5-point scale, similar to the established PI-RADSV2 prostate reporting scoring system used to report MRI. This 5-point scale provides a score of the ultrasound appearance ranging from homogeneous and mid-grey (highly likely to be benign) through to heterogeneous and echo-poor (highly likely to be malignant). Any identified focal areas will be measured and the site documented dependent upon where in the gland the image was taken. Assessment of the presence of Colour flow Doppler will documented on a 3-point scale ranging from no colour Doppler signal evident to florid colour Doppler evident (signal fills the imaging sample box). The scoring system for the standard ultrasound and micro ultrasound images is provided in Appendix 6 (standard) and Appendix 7 (micro). Once reviewed, the scores submitted on the data collection forms will be uploaded onto the database by the lead researcher.

1.5.13 Data collation

Once the reviewers scores have been uploaded onto the database, the lead researcher will review the clinical information taken as part of the standard care consultation. This will include the PSA level and documented DRE report. Both will be added to the database. The MRI report is undertaken

as part of the standard care pathway. The MRI PI-RADS score and documented site of abnormality will be recorded on the data base. The histology results of any prostate biopsies undertaken will also be reviewed and the histological Gleeson score added to the database.

1.5.14 Data analysis

Once the database is complete for each participant, the lead researcher will compare the:

- ultrasound scores
- ultrasound colour Doppler findings
- prostate volume size
- lesion size

The above criteria will be compared between both the standard and micro-US imaging, and then the standard and micro-US with both MRI and histology. An assessment of agreement will be undertaken to evaluate the concordance between the two reviewers of the same images (Ranganathan, Pramesh and Aggarwal 2017). The relationship between these pairs will be evaluated using Bland-Altman plots. Scores from the ultrasound reviews will also be evaluated to determine inter-and intra-operator agreement between the randomly allocated reviewers. The inter-rater reliability, both within and across subgroups of reviewers, will be assessed using the intra-class correlation coefficient or the Cohen weighted kappa test (de Raadt et al. 2021).

1.6 Study design and methodology – Phase 2

Men eligible for AS will be invited to participant in phase 2. A multi-parametric US examination will be undertaken as part of the AS monitoring regime. Men under AS have a prostate serum antigen (PSA) blood test and digital rectal examination every 6 months. A multi-parametric US examination will be undertaken at these appointments to minimise unnecessary health care interactions for the participants. The multi-parametric US examination will be performed blinded to the previous examinations and histology results. The images will be scored and then correlated with previous imaging scores and current PSA levels. Any changes will be indicated to the lead urologist and the patients will be offered MRI imaging to evaluate any changes using existing gold standard imaging.

1.6.1 Phase 2 recruitment

Participants into phase 2 of the study will be invited from the cohort of patients who have already undergone investigations for suspected prostate cancer which include MRI imaging as a requisite. Patients who have low probability MRI scores of PI-RADS 1 or 2 will be invited onto the phase 2 longitudinal arm of the study. Patients who have had biopsy and have either low risk localised

prostate cancer and have elected to be monitored with AS, or those with higher grade disease and who have elected to be monitored via a WW pathway will also be invited on to the phase 2 longitudinal arm of the study.

1.6.2 Sample size phase 2

Again, determining a sample size for this proof of concept study remains difficult. Given the small numbers likely to be recruited into phase 1 and therefore eligible to continue to phase 2, all phase 1 participants who are managed under AS or WW will be invited to continue onto phase 2 of the study with maximum cohort of 30 being accepted. It is acknowledged that inclusion in phase 2 is dependent upon cancer grading at diagnosis and, due to uncertainty of disease diagnosis within the cohort it may be difficult to recruit participants within the two-year time limit for data collection. Participants in phase 1 and 2 will continue to be recruited up to a maximum of 18 months from the commencement of the study to maximise the opportunity for phase 2 recruitment.

1.6.3 Inclusion criteria for phase 2

Men referred to urology within Hull University Teaching Hospitals NHS Trust with known localised prostate cancer of Gleeson 3 + 3 (6) or less and:

- Are eligible for an AS monitoring pathway
- Are on an AS monitoring pathway which is regularly reviewed by a consultant urologist
- Able to attend Castle Hill Hospital for 6 monthly multi-parametric US examinations
- Are able to tolerate a rectal ultrasound examination
- Able to provide informed consent to the study

1.6.4 Exclusion criteria for phase 2

- Men who meet eligibility criteria for active surveillance but have elected to undergo active treatment (hormone treatment, prostatectomy or radiotherapy)
- Men who do not meet eligibility criteria for active surveillance
- Men who are eligible for inclusion but who cannot tolerate rectal ultrasound examinations.
- Men who are unable to consent to the study
- Men who withdraw consent during the longitudinal study
- Men who are unable to attend Castle Hill Hospital for ultrasound imaging within study time frames

1.6.5 Phase 2 recruitment process

Once the initial diagnosis has been made, patients are discussed at the urology prostate multi-disciplinary meeting. A decision is made as to the most appropriate course of treatment is made and, following this, the patients attend for a consultation within a specialist prostate cancer clinic. Biopsy results and MDT outcomes are discussed and the patient is given the advised options for management. For localised low risk disease this does include active surveillance. For patients who may be less eligible for active or even deferred treatment an option of watchful waiting prior to palliative treatment being given can be offered. Providing all patients within these cohorts have had pre-biopsy MRI they are eligible for the study.

1.6.6 Participation and patient contact

Following consultation and treatment choice the eligible patients will be given an information leaflet about the study. The lead researcher will be informed of the patients who have been approached by the specialist nurse. The lead researcher will then contact the patient by telephone and invite them to participate in the study. The phase 2 recruitment pathway is provided in appendix 3. Once verbal consent has been given, a mutually convenient appointment will be made and confirmed with an appointment letter.

The patient will attend for agreed appointment and a face to face consultation with the lead researcher will be undertaken to discuss the study and obtain written consent. The lead researcher will be blinded to the results of the MRI and any previous ultrasound image collection at this time to minimise undue coercion into the study, as in phase 1.

1.6.7 Image collection Phase 2

The ultrasound examination described and image collection for phase 2 is identical to that of phase 1. The exception being that once the images have been collected and stored the patient will be free to leave; no further consultation, procedure or examination will be undertaken.

1.6.8 Data collection phase 2

The data collection of phase 2 is identical to that of phase 1. Data collections forms utilised are attached in Appendix 6 & Appendix 7. The current standard and micro-ultrasound collected as part of phase 2 will be reviewed by two randomly allocated reviewers and scored as outlined above.

1.6.9 Data assessment phase 2

Once scored the documented criteria will be compared between both the standard and micro-US imaging collected during phase 2, and then compared with the previous standard and micro-US imaging collected during phase 1.

1.6.10 Data analysis phase 2

The relationship between these pairs will be evaluated using Bland-Altman plots as per phase 1. Scores from the ultrasound reviews will also be evaluated to determine inter-and intra-operator agreement between the randomly allocated reviewers. The phase 1 images and cine loop are the baseline data that all subsequent phase 2 examinations undertaken on that particular participant will be compared.

Any changes between the initial ultrasound scores and subsequent scores obtained during the longitudinal phase 2 study will be alerted to the lead clinical supervisor (Consultant Urologist) and the patient will be reviewed at the next MDT.

1.7 Phase 3: Staff population

Phase 3 of the study aims to evaluate staff's views about how the novel use of multi-parametric and micro ultrasound impacts on their work, and their expectations about whether it could become a routine part of their clinical practice.

1.7.1 Cohort

Phase 3 participants are invited from the staff population. Sonographers and radiologists involved in the current prostate cancer pathway will be invited to participate in the study.

1.7.2 Data collection tool

Normalization Process Theory (NPT) provides a framework for understanding how a new intervention becomes part of normal practice. A survey aligned with NPT will be used to develop an understanding of the complexity of the work involved in the implementation of using ultrasound within prostate cancer diagnosis and assessment. The survey will be used at the beginning of the study and again at between 6 - 12 months' post commencement to evaluate if perceptions have changed over time. NPT will be used to better understand healthcare practitioners feel about the implantation of new and complex techniques and technology.

1.7.2.1 NPT components

Qualitative data, collection via the survey from participants in phase 3, will be gathered to better understand the following:

- When they use and interpret / score the new technology how familiar does it feel?
- Do they feel that the new technology and interpretation is currently a normal part of their work?
- Do you feel that the new technology and interpretation will become a normal part of their work?

1.7.2.2 NPT domains

The survey will investigate the four domains of NPT. It will investigate the ways that participants make sense of the work of implementing and integrating multi-parametric and micro ultrasound into practice (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring). This phase of the study will evaluate any differences between different grades of staff using ultrasound in this study and between professional groups involved. Skill mix is an important consideration when implementing new techniques or interventions to ensure that these can be successfully integrated into real world clinical practice.

1.7.3 New technology impact assessment

Phase 3 will investigate the impact that differing professional groups may have on developing and implementing new technologies although the small sample size will preclude any quantitative data analysis. A narrative review will be provided.

1.7.4 Phase 3 sample

Participants for phase 3 will be invited from the whole cohort of professionals who work within the radiology team currently involved with prostate imaging within the Hull University Teaching Hospital NHS Trust. This cohort of professionals includes urology specialised radiologists and sonographers who are involved with the production and interpretation of prostate imaging, and will also include urology consultants and urology registrars who are involved with reading and decision making from prostate imaging at multi-disciplinary team meetings. Sonographers in this cohort are radiographers who have undertaken Masters level post graduate training in medical ultrasound and specialised in specific prostate imaging. Relevant staff employed within this service will be given study information leaflets and invited to join the study. The phase 3 cohort will be a maximum of 12 staff members from varying professions.

1.7.5 Conflicts of interest

Whilst it is important to maintain anonymity within this group, this will be difficult to maintain as the numbers of staff within each professional group is small. Data analysis will only be undertaken by the lead researcher and all results will be shared sensitively with consideration that confidentiality will be maintained at all times. Identifiable data will not be published or shared. The lead researcher

who will be involved in the acquisition and scoring of the multi-parametric ultrasound images but will not complete a phase 3 survey to prevent bias. However, the lead researcher will complete a survey independent of the study at implementation and at 12 months and use this to inform their reflection of the study and personal development within their clinical role.

1.7.6 Lead researcher considerations

The lead researcher is a key player in the small clinical team and integral in ensuring NHS service delivery can be maintained. The lead researcher is also the clinical lead sonographer for the ultrasound service within the trust. It is recognised that this may cause unnecessary conflict and bias. To avoid this, and to minimise the risk of coercion consent for participation within phase 3 of the study will be obtain by the recognised PhD clinical supervisor, Mr Matthew Simms, Consultant Urologist, who is overseeing the clinical aspect of the study with the lead researcher. This potential conflict is an acknowledged risk and will be managed by open communication and by ensuring participants have the option to withdraw consent to participate at any time with no adverse effects.

1.7.7 Inclusion criteria for phase 3

- Health care practitioner working as a radiologist or sonographer and employed within radiology of Hull University Teaching Hospitals NHS Trust
- Hold a recognised qualification awarded by the Royal College of Radiologists or a recognised post graduate ultrasound qualification undertaken at a CASE approved higher education institute
- Registered with a statutory regulator such as the GMC, NMC or HCPC
- Participates in the current radiology prostate cancer assessment care pathway
- Able to provide informed consent to the study

1.7.8 Exclusion criteria for phase 3

- Health care practitioners not employed in Hull University Teaching Hospitals NHS Trust
- Sonographers or radiologists not directly participating in the current radiology prostate cancer assessment care pathway
- Sonographers or radiologists who do not hold relevant qualifications listed within the inclusion criteria
- Sonographers or radiologists who do not hold relevant statutory registration
- Sonographers or radiologists who do not consent to participate in the study

1.7.9 Phase 3 data collection

The survey is designed using the tool related to the normalisation process theory. The Normalisation MeAsure Development (NoMAD) tool is a questionnaire of survey items used to assess the

implementation processes of this new technology. A paper copy of the survey questions is provided in Appendix 8. The survey will be created within the JISC (Joint Information Systems Committee) online survey tool and distributed anonymously to all participants; it is acknowledged that anonymity is difficult to maintain due to the small cohort of staff and the wide variety of individual roles.

1.7.10 Phase 3 participant and data confidentiality

Confidentiality will be maintained. The responses will be analysed in a simple tabular format summarising the frequency of responses to items which will indicate where participants are providing more positive or negative responses.

1.7.11 Data analysis

A narrative of the qualitative data collected will be produced to identify the main themes that may provide an opportunity for development or either technology or skill set of the participant as well as identifying the barriers to implementation.

1.8 Phase 4

A fourth phase of the study is planned. Once outcomes from the initial 3 phases of the study are known the lead researcher intends to participate in a national meeting where results will be presented and discussion held between the research team and other centres providing a diagnostic prostate cancer service. The lead researcher has experience of planning and organising national study events and has access to the British Medical Ultrasound (BMUS) Team who will facilitate. The event will be open to all centres providing a prostate service. Notes will be taken during the event to form a narrative of proposed service developments. Attendees at the event will be informed that the event is being undertaken as an outcome of the research study and will be invited to participate in discussions around the study findings and implications for future service delivery.

1.8.1 Inclusion criteria for phase 4

- Delegates attending the specific prostate imaging workshop organised through BMUS
- Able to provide informed consent to the study
- Delegates who are happy to participate in discussion but who do not want their own comments recorded. Reference is made to the Phase 4 consent to study sheet (ICF V2 03.11.2021)

1.8.2 Exclusion criteria for phase 4

- Delegates attending the study event who do not consent to participate in the study

- Delegates who register for the study event but fail to attend. Notes from face to face discussion only will be recorded in the interests of transparency for all participants

1.9 Consent

Written consent will be obtained from all participants in all three phases of the study.

1.9.1 Phase 1 consent

Phase 1 participants will be informed of the study at their initial clinic appointment with a nurse practitioner. A leaflet will be given to the men to read prior to attending for their pre-biopsy MRI examination. Once the MRI has been completed the men will be contacted by telephone and invited onto the study. Those that give verbal consent at that stage will be met by the lead researcher on the day of their routine prostate biopsy appointment and written consent will be obtained.

1.9.2 Phase 2 consent

All histology results post prostate biopsy are currently recorded in the hospital patient information system with the prostate biopsy record. These are discussed at the urology multi-disciplinary meeting and decision to treat or offer active surveillance made. Details of men moving onto AS will be communicated to the lead researcher by the MDT coordinator using a password protected internal hospital database. These men will be contacted by the lead researcher and invited onto phase 2 of the study.

The consent procedure, for both phase 1 and phase 2 of the study, will involve talking to the participant, explaining the aims of the research to them, explaining the aims and objectives of the study, and explain study procedures, and the possibility to withdraw from the study at any given moment without giving any justifications or explanations. The consent form will include permission to continue to use data already collected should a participant withdraw from the study.

Participants will only be included in the study if they are freely able to provide valid consent. Consent forms will discuss the issues related to continued participation in the study should the participant lose capacity and include permission for continuation of data analysis of data that has already been collected should the participant lose capacity to consent.

1.9.3 Phase 3 consent

Phase 3 participants will be invited into the study to both undertake multi-parametric ultrasound imaging, and to provide a retrospective score of the saved images. Phase 3 participants will also be required to undertake 2 surveys to provide their views of the new technology using the NoMAD

survey. The requirements of the study will be fully explained in a leaflet prior to a face to face discussion where written consent will be obtained by the lead researcher. Care will be taken to ensure there is no conflict between the lead researchers research role and her clinical role to prevent coercion of team members participating in the study

1.10 Risks, burdens and benefits

1.10.1 Phase 1

1.10.1.1 Risk

There is minimal risk to patients participating in phase 1 of the study. A trans-rectal ultrasound examination of the prostate will be performed prior to any standard care being undertaken. The standard care for patients with MRI PI-RADS score 3, 4 or 5 is to have a transrectal ultrasound probe inserted into the rectum, the prostate identified and appropriate biopsy sites determined. The majority of men tolerate this procedure well. The multi-parametric US examination will involve a probe being inserted into the rectum, images taken and stored for evaluation later. The probe will then be withdrawn and standard care will commence.

1.10.1.2 Burden

The burden upon the patient is to have two probes separately inserted into the rectum as opposed to once for standard care. The examination time will be extended by a maximum of 10 minutes. The burden is greater for participants with MRI PI-RADS score of 1 or 2. Rectal ultrasound and biopsy is not indicated as part of their standard care pathway and, as such, participation in the study will include a transrectal ultrasound examination that they would not normally receive. Both examinations will take no more than 10 minutes in total and will be planned around clinic attendances to avoid unnecessary visits to the hospital.

1.10.1.3 Benefit

The benefit is that the researcher will gain valuable data in terms of stored ultrasound images that can be correlated to existing gold standard MRI and histology where available. The patients will have the satisfaction of participating in a study evaluating new technology which may lead to better outcomes for future patients. The ultrasound imaging is unlikely to be able to provide diagnostic or prognostic information until a comparative analysis with the gold standards has been performed. However, should any findings of incidental pathology or suspicious appearances be determined during the ultrasound examination these will be alerted to the lead clinician. Any such incidental or suspicious findings will then be discussed at the urology multi-disciplinary meeting (MDT) to determine a management plan. Such findings may result in early detection of potential issues providing a benefit to participants on this study.

1.10.2 Phase 2

1.10.2.1 Risk

There is minimal risk to patients participating in phase 2 of the study. A trans-rectal ultrasound examination of the prostate will be performed prior to any standard care being undertaken. Standard care includes a PSA blood test and a DRE. A multi-parametric US examination will be performed immediately following the regular DRE. It again will involve a probe being inserted into the rectum, images taken and stored for evaluation later. This will be repeated with the micro ultrasound probe. The probe will then be withdrawn and the patient attendance complete. Both examinations will take no more than 10 minutes in total.

1.10.2.2 Burden

There is a greater burden to phase 2. This is an examination over and above standard care. The patient will need to tolerate a rectal ultrasound examination every 6 months. As this new technology is being investigated it is not a diagnostic examination and will not provide diagnostic or prognostic results for the individual participant. The burden of dealing with the unknown will be explained to the participant and access to urology specialists will be available at all times. Should any findings of concern be detected on evaluation of the multi-parametric US these will be alerted to the lead urologist and arrangements for MRI will be made. Any changes on MRI compared to the baseline imaging will necessitate diagnostic biopsy.

1.10.2.3 Benefit

The benefit is that the researcher will gain valuable data in terms of stored ultrasound images that can be correlated to previous multi-parametric US, previous existing gold standard MRI and histology where available. The patients will have the satisfaction of participating in a study evaluating new technology which may lead to better outcomes for future patients. The ultrasound imaging is unlikely to be able to provide diagnostic or prognostic information until a comparative analysis with the gold standards has been performed. However, should any findings of incidental pathology or suspicious appearances be determined during the ultrasound examination these will be alerted to the lead clinician. Any such incidental or suspicious findings will then be discussed at the urology MDT to determine a management plan. Such findings may result in early detection of potential issues providing a benefit to participants on this study.

1.10.3 Phase 3

1.10.3.1 Risk

There is minimal risk to health care practitioners participating in phase 3 of the study. There is an established group of sonographers and radiologists providing the radiology prostate cancer assessment care pathway. There is a risk to the study of attrition of participants due to the age

demographics of the available workforce and staff relocating. There is also a risk of conflict between professional groups as knowledge and skills develop. This will be mitigated by regular communication with the study groups, led by the lead researcher and supported by the academic supervisory team as a non-involved third party. The greatest risk however is due to the lead researcher having a pivotal leadership role within the team and crucial to normal service delivery. There is a risk of unintentional bias from participants either feeling they should participate or feeling the need to please. These risks will be mitigated by open and honest communication with all team members upon recruitment and during the study.

1.10.3.2 Burden

There is a burden on the participants in phase 3; this is an additional workload over and above their existing activity. However, the ultrasound department is highly supportive of research and development and allocates time for such activity within practitioners' working day. There is a risk that the radiologists may have competing workloads which cannot be mitigated against but, again, R&D is supported within radiology and this study provides development opportunities for all participants.

1.10.3.3 Benefit

The participants will have the opportunity to learn new skills and improve their knowledge of this common disease. They will be participating in a study with the aim of improving patient care in their chosen field of practice. This will, hopefully, engender professional pride, engagement, and commitment. The participants will have the opportunity to use and experience new ultrasound technology. This study is using the first micro-ultrasound machine installed in the UK and, as such, is ground breaking in the UK knowledge of prostate ultrasound imaging.

1.10.4 Phase 4

Phase 4 of the study requires the organisation of a study event. There will be little in terms of burden on the participants of this event; indeed, it is likely to be hugely beneficial in terms of sharing practice and hearing about new technology. The burden will be on the lead researcher who will be responsible for organising the event and ensuring an accurate record of discussions in transcribed. However, there are benefits of discussion with other health care providers ensuring the research does not become single centre-centric and to provide a wider overview of practice that could be implemented to better improve local services.

1.11 Confidentiality

This project is a prospective study comprising data from the medical records of patients of Hull University Teaching Hospitals NHS Trust, who in keeping with standard clinical care and management, have undergone diagnostic tests, treatments and interventions but who will be consenting to additional diagnostic imaging examinations. Therefore, in accordance with the Health Research Authority (2017), this study requires approval from the Local Research Ethics Committee (LREC). As this study is being undertaken as part of a PhD programme, ethical release has been sought from the University of Hull.

1.12 Approval

Approval from the Hull University Teaching Hospitals NHS Trust will be sought in line with the local Research And Development Operational Policy which is in place to ensure studies adhere to a robust ethical framework. Key to this is legislation in the Data Protection Act (2018), General Data Protection Regulations (Gov.UK, 2018) and the guidance upheld in the Caldicott Principles 1997.

Wherever possible sensitive and personal information, which may identify participants, will be removed to minimize the risk of data breaches. The Hull University Teaching Hospitals NHS Trust data protection policy and procedures will ensure possible data breaches are risk assessed and that protection of network drives are maintained and kept current. Unnecessary data will not be stored.

1.13 Data security

All data will be collected within the following restrictions:

Only the data required for the evaluation of the study aims and objectives will be collected. All data will be accurately transcribed and analysed within the confines of the requirements of the project. The data will be utilised for the specific purpose of this study only. Consent forms will include permission for data access by the primary research team, use of data in publication as well as consent for future studies which may originate from this primary study.

New and emerging technology is used in this study and as such new diagnostic features may become evident. As such intellectual property rights are considered and advice is sought from the Hull University Teaching Hospitals NHS Trust IP team.

1.13.1 Incidental or adverse clinical findings

Consideration is given to incidental pathology or suspicious findings detected as part of the imaging component undertaken during the diagnostic data set collection within this study. The consent

forms will include permission for the researcher to share any abnormal findings or concerns about suspicious findings with the participant's clinical team to avoid unnecessary delay to diagnosis and / or clinical treatment.

1.14 Conflict of interest

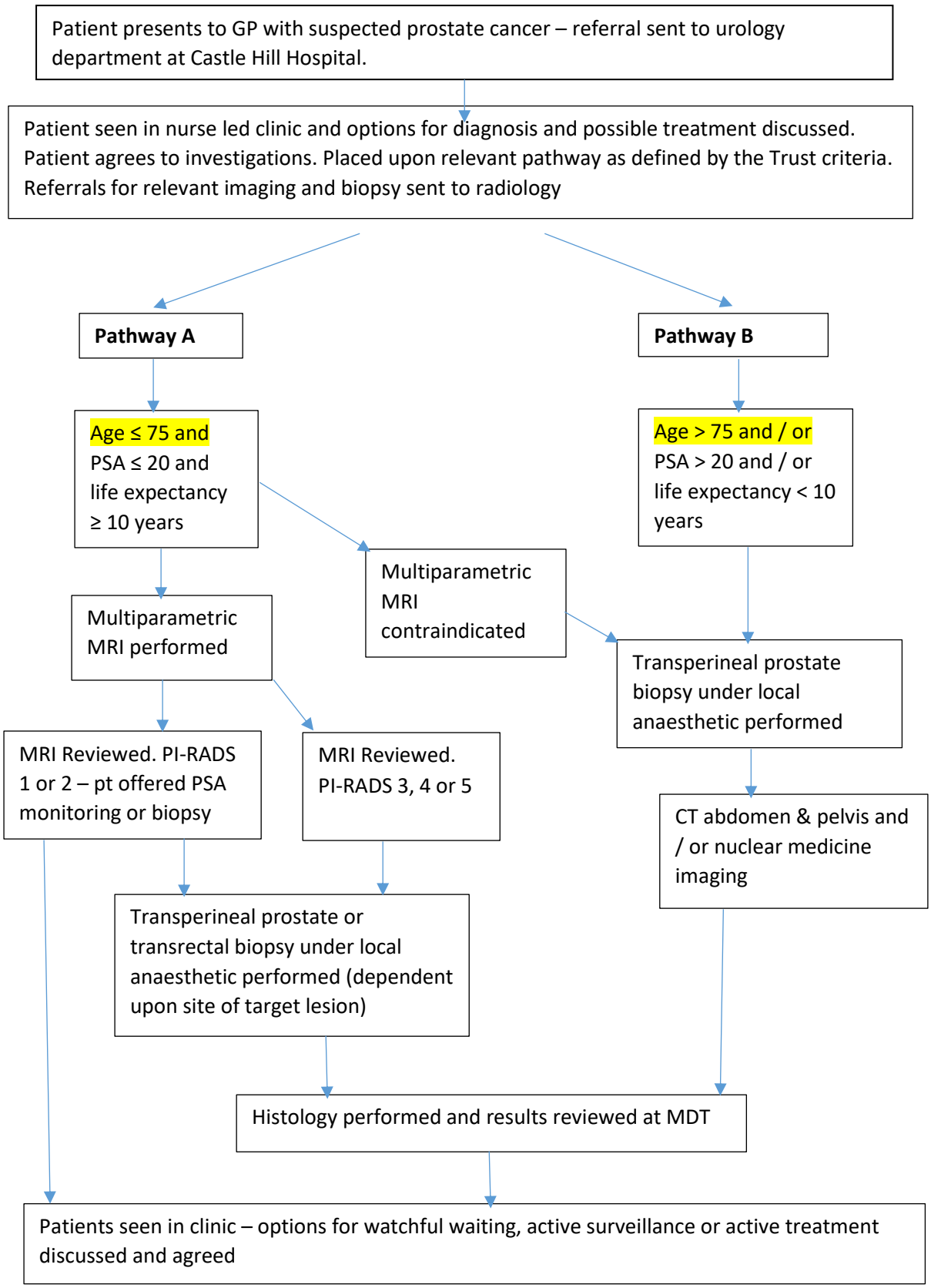
The major conflict of interest is that the lead researcher is a sonographer and will be going through a period of skill development as per the participants in phase 3 of the study. Robust supervision will mitigate against undue bias during the phase 3 data collection and analysis.

Participants may request access to data relating to their own input into the study and will be given access to their own record only. No other participant data will be shared.

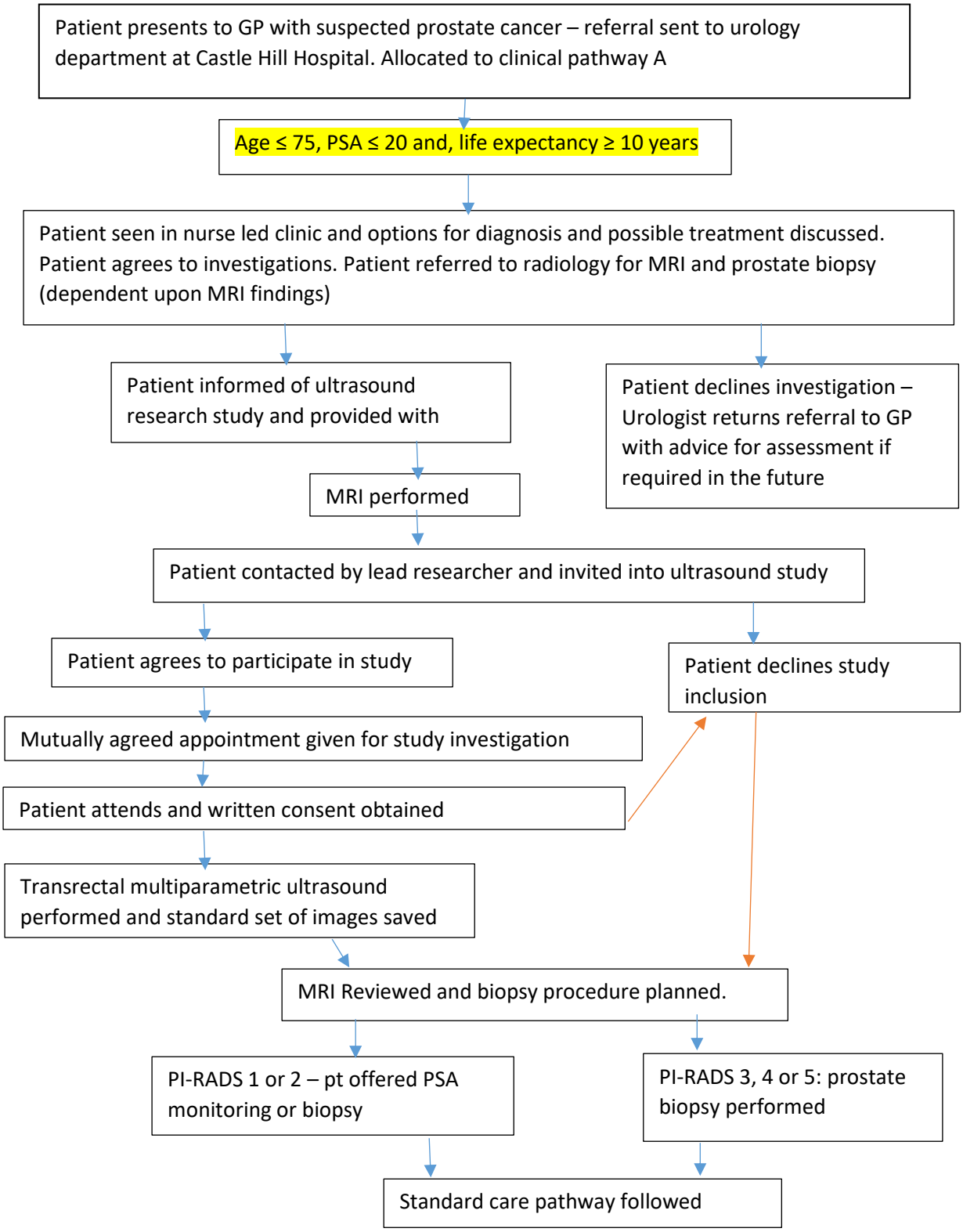
1.15 Use of tissue samples in future research

No human tissue will be stored for future research. All stored data related to this study, including images and databases, will be destroyed after 10 years in compliance with the Hull

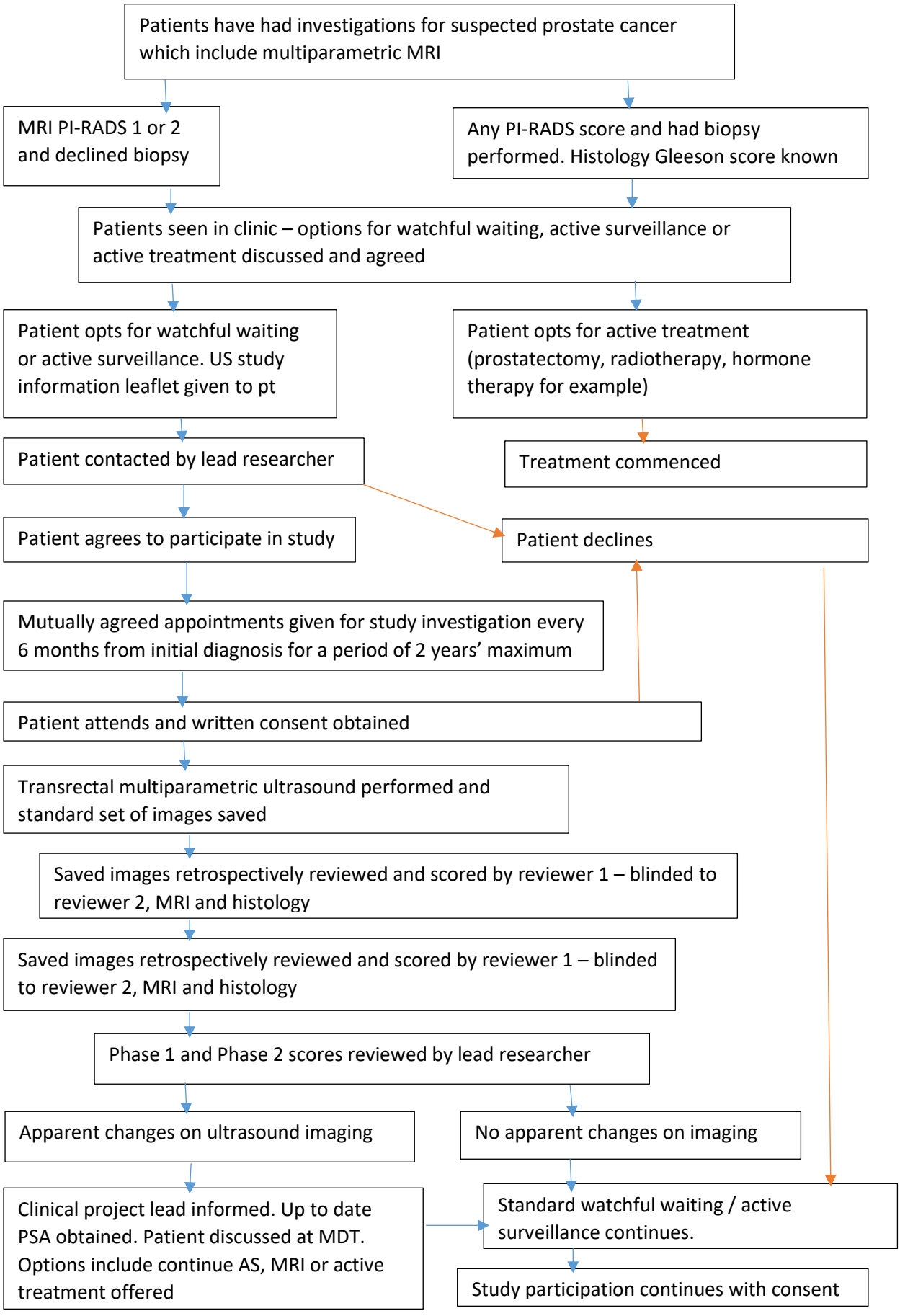
1.16 Appendix 1: Evaluating the role of diagnostic ultrasound in prostate cancer – Current clinical pathway. Referral to diagnosis



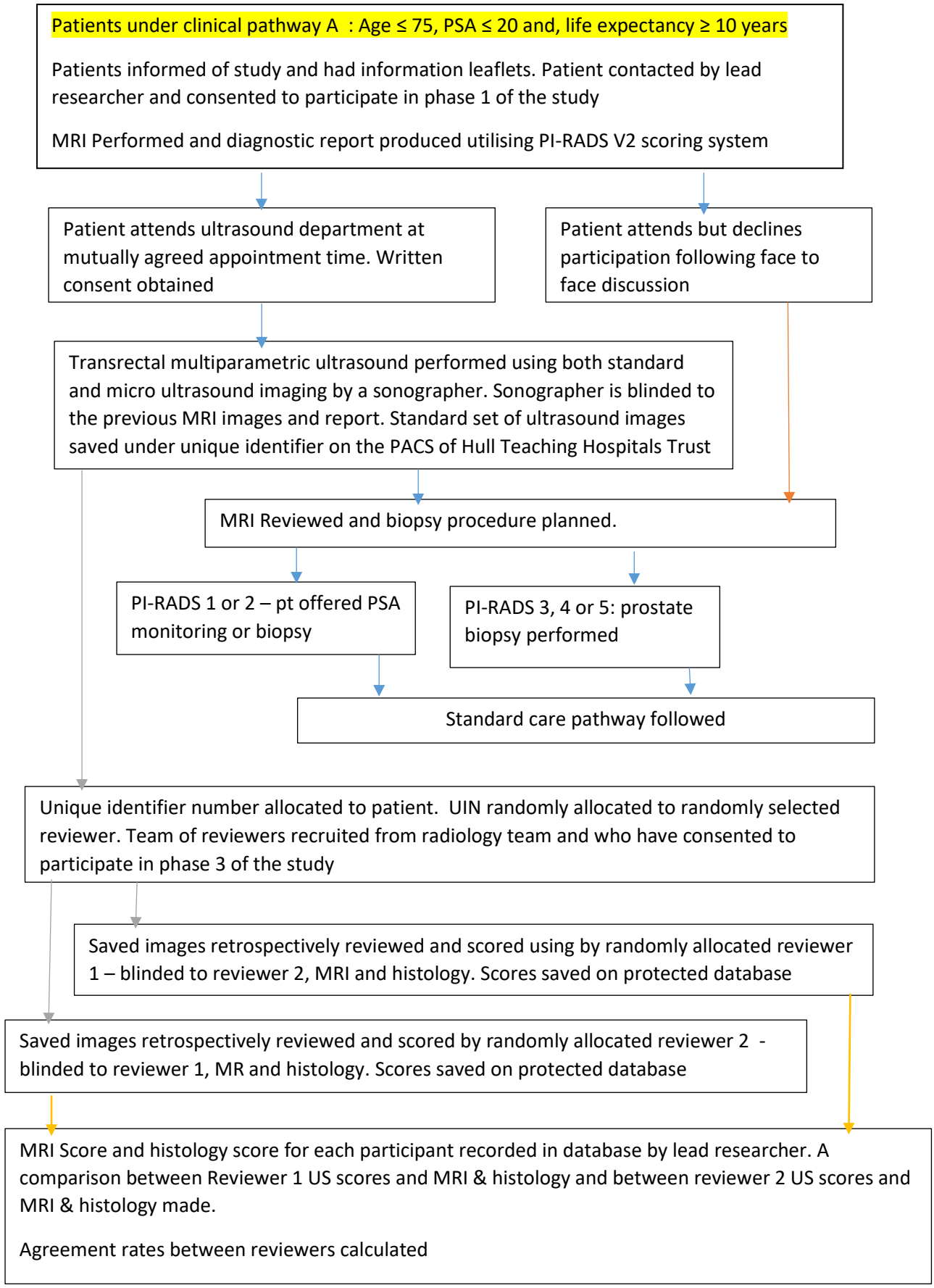
1.17 Appendix 2: Evaluating the role of diagnostic ultrasound in prostate cancer – Phase 1 recruitment



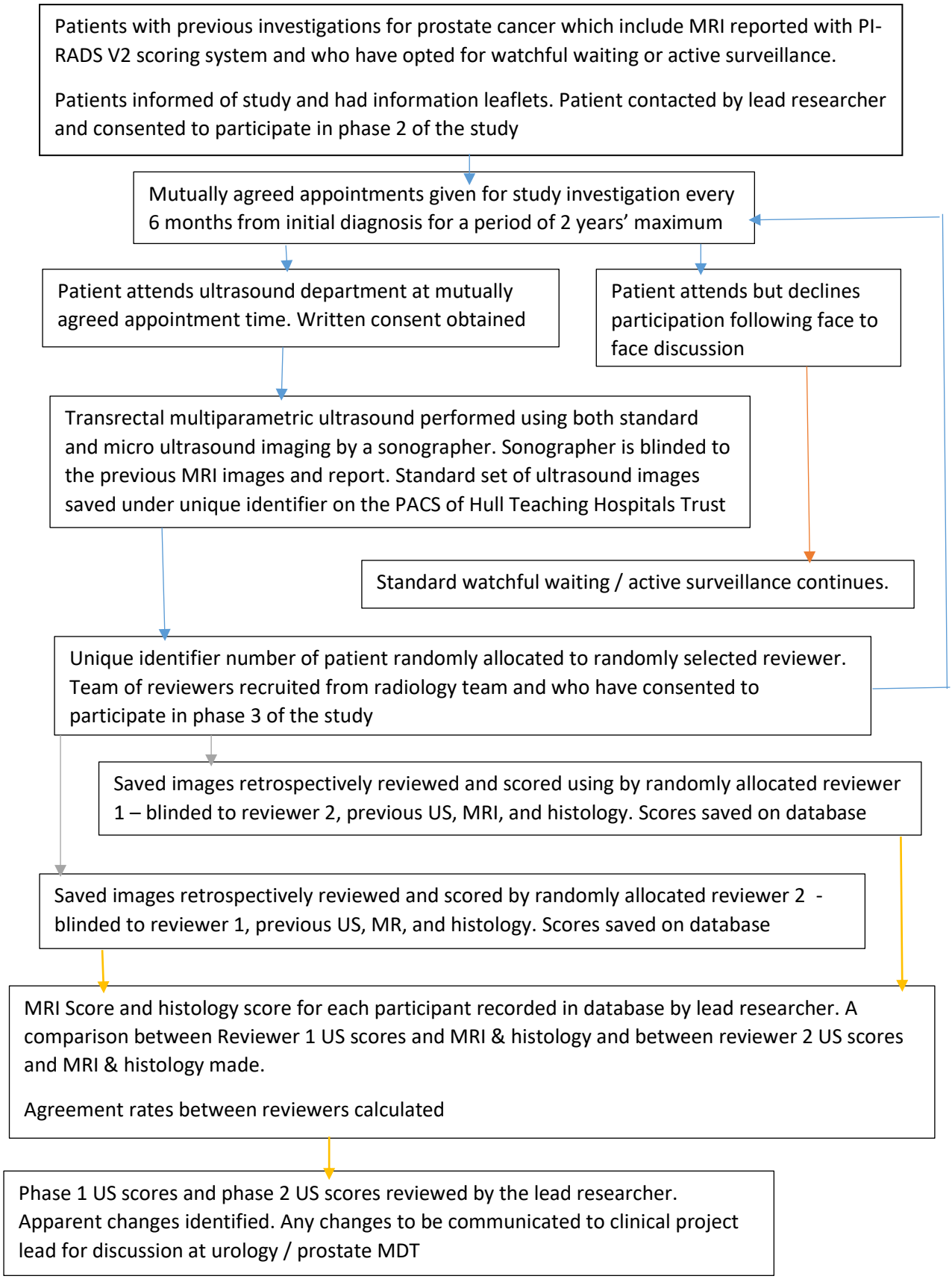
1.18 Appendix 3: Evaluating the role of diagnostic ultrasound in prostate cancer – Phase 2 recruitment



1.19 Appendix 4: Ultrasound in prostate cancer – Phase 1 Image review pathway



1.20 Appendix 5: Diagnostic ultrasound in prostate cancer – Phase 2 Image review pathway



1.21 Appendix 6: Data collection form – Standard Ultrasound

Appendix 6: Data Collection form- Standard Ultrasound

ERUP Study Data Collection Form

Lead Researcher only	Participant number:	
	Phase 1	Phase 2

Reviewer: Please circle 1 2 3 4 5 6

Date of Review:

Imaging Reviewed:

Standard US	Date of Scan

Cine Loop Images

Please indicate findings of both longitudinal sweep and transverse sweep:

Longitudinal Sweep	Findings:	Transverse Sweep	Findings:
Opinion of prostate on review of cine loop	No apparent abnormality	Opinion of prostate on review of cine loop	No apparent abnormality
	Uncertain		Uncertain
	Normal BPH nodule (s)		Normal BPH nodule (s)
	Atypical focal area (s)		Atypical focal area (s)
If lesion identified, please indicate approximate site	Rt Lateral	If lesion identified, please indicate approximate site	Right Base
	Rt Mid		Left Base
	Central/midline		Right Mid
	Lt Mid		Left Mid
	Lt Lateral		Right Apex
			Left Apex

Approximate Prostate Volume:		
Length (cm)		
Height (cm)		
Width (cm)		
Volume:	x 0.53	

Unable to calculate? State reason:

ERUP Data Collection Schematic: Standard US V1 09.08.2021

1.22 Appendix 7 – Data collection form – Micro-ultrasound

Appendix 7: Data Collection form- Micro Ultrasound

ERUP Study Data Collection Form

	Phase 1	Phase 2

Reviewer: Please circle 1 2 3 4 5 6

Date of Review:

Imaging Reviewed:

Micro US	Date of Scan

Cine Loop Images

Please indicate findings of both longitudinal sweep and transverse sweep:

Longitudinal Sweep	Findings:	Transverse Sweep	Findings:
Opinion of prostate on review of cine loop	No apparent abnormality	Opinion of prostate on review of cine loop	No apparent abnormality
	Uncertain		Uncertain
	Normal BPH nodule (s)		Normal BPH nodule (s)
	Atypical focal area (s)		Atypical focal area (s)
If lesion identified, please indicate approximate site	Rt Lateral	If lesion identified, please indicate approximate site	Right Base
	Rt Mid		Left Base
	Central/midline		Right Mid
	Lt Mid		Left Mid
	Lt Lateral		Right Apex
			Left Apex

Approximate Prostate Volume:		
Length (cm)		
Height (cm)		
Width (cm)		
Volume:	x 0.53	

Unable to calculate? State reason:

ERUP Data Collection Schematic: Micro US V1 09.08.2021

1.23 Appendix 8 – Phase 3 Implementation Survey

Appendix 8 – Phase 3 Implementation Survey

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Implementation of new technology into clinical practice survey

This survey is designed to help get a better understanding of how to apply and integrate new technologies and complex interventions in health care.
This survey asks questions about the implementation of **micro-ultrasound in prostate imaging. We understand that people involved with prostate imaging have different roles, and that people may have more than one role.**

From the statements below please choose an option that best describes ***your main role*** **in relation to micro-ultrasound in prostate cancer assessment:**

I am, or will be, involved in managing micro-US in prostate assessment ☐
I am, or will be, involved in performing micro-US and prostate imaging ☐
I am, or will be, involved in the interpretation of micro-US as radiologist or at MDT ☐

For this survey, please answer all the statements from the perspective of the role you specify. Depending on your role or responsibilities in relation to micro-ultrasound, some statements may be more relevant than others.

The survey is in 3 parts. Part A asks some brief questions about yourself and your role. Part B includes three general questions about **micro-ultrasound and prostate imaging;** Part C contains a set of more detailed questions about **micro-ultrasound and prostate cancer assessment.** For each statement in Part C, there is the option to agree or disagree with what is being asked **(OPTION A).** However, if you feel that the statement is not relevant to you, there are also options to tell us why **(OPTION B).**

Please take the time to decide which answer best suits your experience for each statement and tick the appropriate box

Part A: About Yourself

Question 1:
Please provide your professional background:

Sonographer	
Consultant Radiologist	
Radiology Registrar	
Consultant Urologist	
Urology Registrar	
Would rather not say	

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