FULL PROTOCOL TITLE OF THE STUDY

Sexual Assessment after Focal therapy with various Energy sources: a mixed methods study

SHORT STUDY TITLE / ACCRONYM

Sexual Assessment after Focal Energy treatment/SAFE study

Study team:

Chief investigator**:** Mrs Gaelle Fiard, MD, PhD
Research Fellow, Division of Surgery and Interventional Science, UCL
Department of urology, UCLH NHS Foundation Trust, London

Supported by:
Fondation de France
European Urology Scholarship Program
Angiodynamics

Sponsored by:
University College London (UCL)

Protocol version number and date:
Version 1.0, 29/06/2020

R&D / Sponsor Reference Number(s):
129786

Study Registration Number:
Z6364106/2020/02/48

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	1.0	29/06/2020	Gaelle Fiard	Ethics submission

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature: **Date 29/06/2020.**

Print Name(in full): Gaelle Fiard

Position: Research Fellow

On behalf of the Study Sponsor:

Signature:.. **Date: 01/07/2020**

Print Name(in full): Delasi Apraku

Position: Sponsorship Officer

STUDY SUMMARY

Identifiers	
IRAS Number	278558
REC Reference No	
Sponsor Reference No	129786
Other research reference number(s) (if applicable)	Z6364106/2020/02/48
Full (Scientific) title	Sexual Assessment after Focal therapy with various Energy sources: a mixed methods study
Health condition(s) or problem(s) studied	Prostate cancer
Study Type i.e. Cohort etc	Qualitative research, questionnaire, interview or observation study
Target sample size	50 20 patients in the retrospective cohort 30 patients in the prospective cohort
STUDY TIMELINES	
Study Duration/length	6 months
Expected Start Date	September 2020
End of Study definition and anticipated date	The study will end after the last patient recruited has completed his 3 months semi-structured interview. (Anticipated February 2021)
Key Study milestones	Study submission: June 2020 Budget/contract finalised: June 2020 First patient recruitment: September 2020
FUNDING & Other	
Funding	Fondation de France European Urology Scholarship Program Angiodynamics
Other support	
KEY STUDY CONTACTS	Full contact details including phone, email and fax numbers
Chief Investigator	Gaelle Fiard Department of Targeted Intervention Division of Surgery & Interventional Science University College London Floor 3, Charles Bell House 43-45 Foley Street London W1W 7TY Email: g.fiard@ucl.ac.uk Phone: 07568764334
Co-investigator:	Professor Mark Emberton, FRCS(Urol), FRCS, MD, MBBS, BSc Division of Surgery and Interventional Science, UCL Department of urology, UCLH NHS Foundation Trust, London Suite 1A, Maple House, 149 Tottenham Court Road, London W1T 7NF Email: m.emberton@ucl.ac.uk

	Phone: 0207 679 5208
Co-investigator:	Professor Daniel Kelly FRCN Royal College of Nursing Chair of Nursing Research School of Healthcare Sciences, Cardiff University Eastgate House Newport Road Cardiff CF240AB Email: KellyDM@cardiff.ac.uk Phone: 029 2087 4000
Co-investigator	Mr Tet Yap, MA, MD, FRCS Department of urology, Guy's and St Thomas' NHS Foundation Trust, London Guy's Hospital Great Maze Pond, London, SE1 9RT Email: Tet.Yap@gstt.nhs.uk Phone: 07780611631

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

KEY WORDS

Prostate cancer, focal therapy, erectile dysfunction, sexual function

LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
HIFU	High Intensity Focused Ultrasound
IB	Investigator Brochure
ICF	Informed Consent Form
IIEF	International Index of Erectile Function
IPSS	International Prostatic Symptom Score
IRE	Irreversible Electroporation
MRI	Magnetic Resonance Imaging
MSHQ-EjD-SF	Male Sexual Health Questionnaire – Ejaculatory Dysfunction-Short form
PI	Principle Investigator
PIS	Participant Information Sheet
PROs	Patient-Reported Outcomes
PSA	Prostatic Specific Antigen
REC	Research Ethics committee
RFS	Recurrence-free survival
SAE	Serious Adverse Event
SDV	Source Data Verification
SF 12	Short-form 12
SOC	Standard Of Care

CONTENTS

1 INTRODUCTION

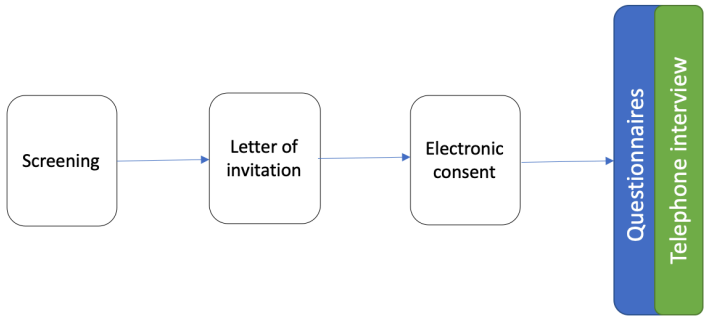
Over the last decade, despite progress in surgical techniques (robotics) and perioperative management (medication), men's ability to recover erectile function after radical prostatectomy has not improved. Over the last decade, the proportion of men who are able to recover erectile function within 24 months after surgery has remained a constant 30% [1]. During this same period, progress in magnetic resonance imaging of prostate cancer has enabled the emergence of both image-guided biopsy and treatments. This novel diagnostic and therapeutic pathway has conferred a step-change in likelihood that men will experience little, if any, deterioration in their genito-urinary function as a result of their prostate cancer diagnosis and treatment[2].

Whilst the stability of mens' genito-urinary functional status through the process of treatment is something to be celebrated, most of the evaluation of function has taken place at a relatively high, non-granular level. Most of the data we use to provide informed consent for our patients is obtained from retrospective – usually single-centre – series, or derived from prospective studies whose primary outcome was oncological [3].

Moreover, these studies have –to a very large extent - focused exclusively on erectile function. Other, presumably important, elements of male sexual function (orgasmic sensation, ejaculatory function, penile length and shape, climacturia) have been largely overlooked. There have been some notable exceptions, such as the careful morphometric analysis of penile function following high-intensity focused ultrasound and cryotherapy [4]. However, we have hardly any insight into the detailed consequences of some of the newer energy sources (such as irreversible electroporation) that are being used to treat the prostate in a tissue-selective manner [5]. Qualitative research methods enable in-depth exploration of a predefined domain and have already been used to collect patients' sexual recovery after whole-gland treatment [6].

The SAFE study will, therefore, aim at eliciting detailed sexual outcomes after focal therapy, focusing on the early postoperative status. The study will comprise two cohorts: a retrospective cohort of patients treated with focal irreversible electroporation, and a prospective cohort of patients treated with 3 focal therapy energies. The retrospective cohort will consist in 20 sexually-active patients treated by IRE in the last 24 months. Upon consent, a semi-structured telephone interview will be offered to precise qualitative outcomes at various time points after surgery.

All contemporary consecutive patients treated by focal HIFU, focal cryotherapy and focal irreversible electroporation (IRE) will be offered to participate in the prospective part of the study. Upon informed consent, baseline sexual function, prostate cancer and treatment characteristics will be recorded using validated patient-reported outcome (PRO) questionnaires and a semi-structured telephone interview (before). Follow-up patient PRO questionnaires will be registered at 3 months. A semi-structured telephone interview will be offered at 3 months to collect qualitative sexual outcomes. Study flow-charts are presented in **Figure 1**. Both cohorts will be studied in parallel.



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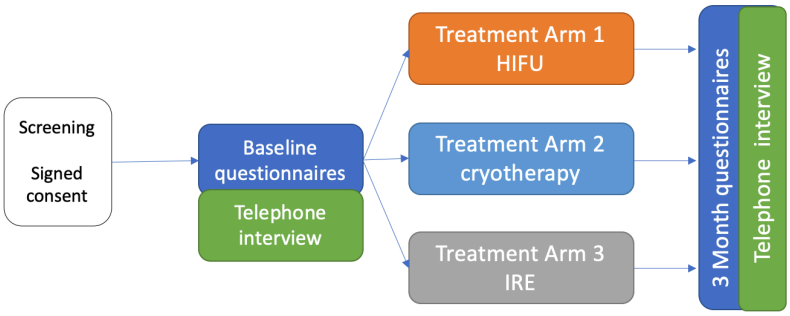


B.

Figure 1. Study flowcharts (A. Retrospective cohort – B. Prospective cohort)

2 BACKGROUND AND RATIONALE

Prostate cancer is a primary concern of public health in the UK with 1 in 6 UK males diagnosed with prostate cancer in their lifetime [7]. Nowadays, 60% of the cases are diagnosed at an early, localised, curable stage, thanks to screening using PSA and imaging with MRI. Although there has been in the past concern about overdiagnosis and overtreatment driven by these screening tests, active surveillance is now offered widely for insignificant disease and allows men with small, non-aggressive prostate cancer to have their treatment (and treatment side effects) differed at the time of progression [8]. Clinically significant prostate cancer car be effectively cured at an early stage by radical, whole-gland treatments such as radical prostatectomy, external or internal-beam radiotherapy [9]. However, these treatments are also known for causing side-effects, such as urinary incontinence and erectile dysfunction, significantly altering the quality-of-life [10].

Precision in the diagnosis, staging and risk stratification of the disease has significantly improved, allowing for the development of focal therapy. Many studies have aimed at describing these new techniques, reporting their oncological and functional outcomes in terms of urinary and sexual function. Although long-term follow-up is still missing for the most recent techniques, focal therapy has proven its oncologic safety at the price of close monitoring and a significant retreatment rate [11].

Failures can be managed by radical salvage treatment options [12, 13]. This risk, even if limited, has to be balanced by a significant improvement in other domains, i.e. urinary and sexual function. Urinary outcomes of radical treatment are improving with the development of new surgical techniques and image-guided therapy, with most recent studies reporting low rates of incontinence or urinary bother. However, the patient-reported outcomes regarding sexual function still underline the need for alternative treatments when sexuality preservation is a priority for the patient [14]. Still, current data available on the sexual function after focal therapy often derive from studies whose primary outcome was the oncological outcome. Series reporting initial results often comprise very heterogeneous cancer stages, older patients, more patients with pre-existing erectile dysfunction or larger volumes of tissue ablation, as well as the learning curve of the operator. Qualitative research methods enable in-depth exploration of a predefined domain and have already been used to collect patients' sexual recovery after whole-gland treatment [6].

The present mixed methods study will address this need by evaluating qualitative sexual outcomes after three different focal therapy modalities, to elicit the evolution of the sexual function of preoperatively potent patients in the early post-operative period (3 months) and at various post-operative time points. Such an evaluation appears of importance to provide the patient with accurate and up-to-date data to put in the harm-benefit balance at the time of treatment decision-making.

The retrospective arm of the study will allow us to obtain in-depth details of the evolution of the sexual function of patients at various time points up to 2 years after surgery. This cohort of patients will be able to provide perspective and be more likely to be relieved of the stress related to the oncological outcome. However, since there will be a significant time gap between the event and the interview, we also decided to include patients prospectively, to ensure the collection of in-depth sexual patient's experiences as they are experiencing them. The PRO questionnaires will allow for a further description of the study population and help position and compare the results obtained with other, mostly quantitative, studies.

3 OBJECTIVES

3.1 Primary Objective

Qualitative sexual outcomes collected during semi-structured telephone interviews at 3 months after focal therapy with HIFU, cryotherapy and IRE.

3.2 Secondary Objectives

Preoperative expectations and patients' priorities

Patient-reported sexual outcome scores (IIEF 15, MSHQ-EjD-SF)

Qualitative sexual outcomes obtained at various time points after treatment with IRE (retrospective cohort).

4 STUDY DESIGN and METHODS of DATA COLLECTION and DATA ANALYSIS

This study will be a mixed methods research study based on a retrospective and a prospective cohort.

4.1 Retrospective cohort

Preoperatively potent patients treated with IRE in the last 24 months will be sent an invitation letter. Upon electronic consent, semi-structured telephone interviews will be offered to gather qualitative outcomes at various time points after surgery. The cohort will be selected purposely so as to represent a variety of post-operative time points. Questionnaires will be self-administered prior to the telephone interview using the REDCap application in the UCL Data Safe Haven and stored in the Safe Haven.

Interviews will be conducted by the same interviewer using a predefined interview guide. Interviews will be recorded using dedicated hardware and transcribed. A thematic analysis will be performed manually and using a software (NVivo version 12) by two members of the research team. All steps will be processed and verified by the research team involving a qualitative researcher and an andrologist. We aim at recruiting 20 patients for this retrospective cohort. Interviews will be conducted in parallel of the recruitment for the prospective part of the study.

Follow-up phone calls

Upon consent, follow-up phone calls will be performed if new themes arise from the first interviews and result in an amendment of the topic guide.

4.2 Prospective cohort

In parallel, all patients presenting with localised prostate cancer accessible to focal therapy with HIFU, cryotherapy or IRE will be screened for participation in the prospective cohort of the study.

Enrolment will be possible providing preoperative potency (erections sufficient for penetration), electronic consent and sufficient knowledge of English to fill-in the self-administered questionnaires.

A baseline evaluation will consist in self-administered validated PRO questionnaires (IIEF-15, MSHQ-EjD-SF) and a semi-structured telephone interview to record baseline status and expectations before surgery. Questionnaires will be self-administered prior to the telephone interview using the REDCap application in the UCL Data Safe Haven and stored in the Safe Haven.

Once the baseline evaluation is completed, patients will proceed with the allocated treatment (physician's choice of therapy arm).

A follow-up clinical visit will be performed at 3 months as per Standard Of Care (SOC). PRO questionnaires will be completed and qualitative methods will be used to gather post-operative sexual outcomes, with in-depth semi-structured telephone interviews. Areas covered will include changes in: erection, ejaculation, orgasm, climacturia, pain/discomfort, libido/sexual desire, masculinity/virility, treatments taken/help, penile morphology, other symptoms, regret, shame, cancer-related stress, overall and partner satisfaction.
Interviews will be conducted by the same interviewer using a predefined interview guide. Interviews will be recorded using dedicated hardware and transcribed. A thematic analysis will be performed manually and using a software (NVivo version 12) by two members of the research team. All steps will be processed and verified by the research team involving a qualitative researcher and an andrologist. We aim at recruiting 10 sexually-active patients in each treatment group, to result in a prospective cohort of 30 patients. Questionnaires will be self-administered prior to the telephone interview using the REDCap application in the UCL Data Safe Haven and stored in the Safe Haven.

Follow-up phone calls
Upon consent, follow-up phone calls will be performed if new themes arise from the first interviews and result in an amendment of the topic guide.

4.3 Data transcription

Recordings will be transcribed by an experienced transcriber from HW secretarial services, Bristol, UK, provided with de-identified interview recordings and upon signing a confidentiality agreement. Transcription will be performed shortly after the interview and all transcripts will be checked for completeness and accuracy by two members of the study team.

4.4 Data coding

Analysis will start with a full-reading and discussion between two of the researchers to support the organisation of the interview transcripts. Codes will be developed in the process of defining clusters and identifying recurring and less usual themes. Data will be coded and comparisons made across the transcripts.

5 STUDY SCHEDULE

Both parts of the study will be conducted in parallel. The timeline of the study is presented in the Gantt chart in **Figure 2**.

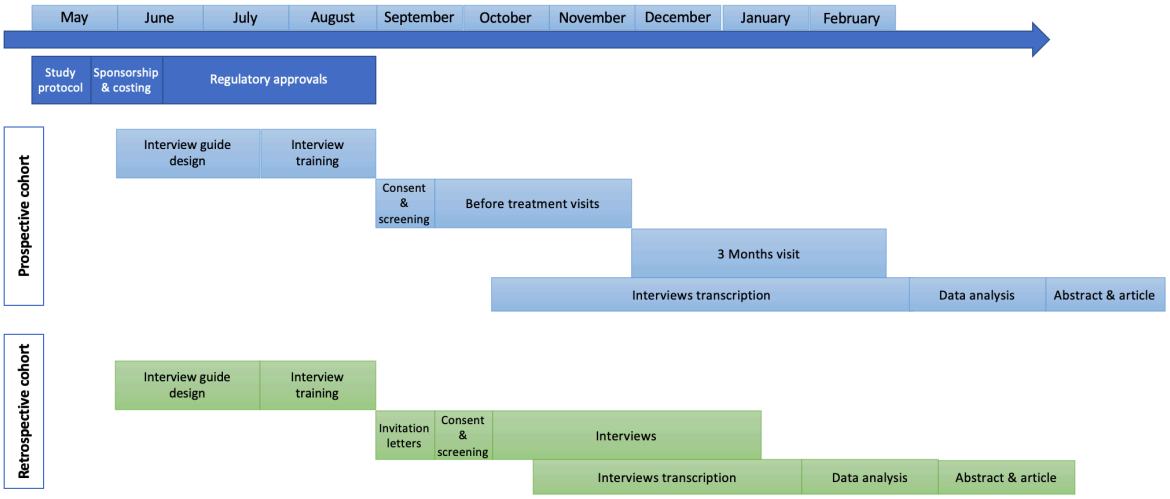


Figure 2. Gantt chart

The study will end after the last patient included has completed the semi-structured interview at 3 months. The planned duration of the study is 6 months.

Participants in the retrospective study will be in the study between signing electronic consent form and interview (expected between 7 days-1 month)

Participants in the prospective cohort will be in the study for 3 months +/- 7 days.

6 CONSENT

The consenting process will be conducted remotely, except for patients in the prospective arm who will be able to directly discuss the study during their planned clinical visits. No in-person visit for consenting purposes will be performed outside of planned standard-of-care clinical visits. After initial signature of the electronic consent form, consent will be continuously sought at each questionnaire administration or telephone interview using a dedicated tick box or question.

Retrospective cohort

For the retrospective part of the study, patients treated in the past 24 months by IRE will receive an invitation letter. If they agree to take part, a Participant Information Sheet (PIS) will be sent by email or regular mail, and a telephone call will be organised to talk them through the different phases of the study, answer potential questions and verify their ability to consent.

Upon agreement, the consenting phase will be performed using the REDCap application in the UCL Data Safe Haven using an electronic Patient Consent Form with tick boxes and simple electronic signature. All documents will be stored in the Data Safe Haven.

Prospective cohort

For the prospective part of the study, patients will be invited to take part in the study during the clinical surgery planning visit and a Participant Information Sheet (PIS) will be given or sent later by email or regular mail. A telephone call will be organised to talk them through the different phases of the study, answer potential questions and verify their ability to consent.

Upon agreement, the consenting phase will be performed using the REDCap application in the UCL Data Safe Haven using an electronic Patient Consent Form with tick boxes and simple electronic signature. All documents will be stored in the Data Safe Haven.

The PIS will support the consent process by helping to ensure that all those who are invited to take part in the study have been adequately informed. It will allow potential participants to make an appropriate decision that is right for them.
The PIS also provides potential participants with information to share with others who may be important to them, and who they would like to involve in the decision-making process.
The PIS will also form part of the transparency information that Data Controllers will also provide potential research participants, under the General Data Protection Regulation (GDPR).

The two Participant Information Sheets (one for each part of the study) and Consent Form will be written in English.

Non-English speakers and readers will be excluded from this study as English-reading is necessary for the completion of questionnaires and these questionnaires have not been validated in other languages. Vulnerable patients without capacity to consent will also be excluded of the study since they probably will be unable to reliably fill self-administered questionnaires. Patients will remain free to withdraw from the study at any time upon demand.

A minimum of 24 hours will be allowed for participants to consider fully the implications of taking part in the present study.

If a participant loses capacity to consent during the study, the participant and all identifiable data would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained. De-identified transcripts may be used by the research team if the transcription has already been performed.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

7.1.1 Retrospective cohort

- Men treated with focal IRE in the last 24 months agreeing to be approached after receiving the invitation letter
- Preoperative normal sexual function (retrospective)
- Signed informed consent by patient

7.1.2 Prospective cohort

- Men with a histological diagnosis of prostate cancer on trans-rectal or transperineal template prostate biopsies
- Gleason score ≤7
- Clinical stage ≤T2cNoMo (radiological T3a allowed)
- Serum PSA ≤15ng/ml
- Local staging imaging as per guidelines to demonstrate localised disease (this may include MRI, CT, bonescan or functional imaging)
- MRI-visible unilateral or anterior disease accessible to focal HIFU, cryotherapy or IRE
- Baseline potency with erections sufficient for penetration
- Signed informed consent by patient

7.2 Exclusion Criteria

7.2.1 Retrospective cohort

- Men with preoperative (remembered) altered sexual function or no sexual activity
- Salvage treatment
- Non-English readers and speakers
- Vulnerable men unable to provide informed consent

7.2.2 Prospective cohort

- Men with baseline erectile dysfunction and erections insufficient for penetration
- Men who had prostate surgery for cancer control e.g., radical prostatectomy, HIFU, cryosurgery, photodynamic therapy
- Men undergoing whole-gland treatment
- Non-English readers and speakers
- Vulnerable men unable to provide informed consent

7.2.3 Sampling

Purposive sampling will be performed for the retrospective cohort to interview patients at various time points after surgery. Patients in the prospective cohort will be consecutive.

8 RECRUITMENT

Only members of the existing clinical care team will access to patient records to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients.

Transparency information about legal basis and other details of processing personal data will be given to patients as recommended by the GDPR from 25 May 2018.

8.1.1 Retrospective cohort

All men treated with focal primary IRE during the last 24 months in Prof Mark Emberton's private practice will be sent an invitation letter. Upon agreement, patients will be contacted by the research team with a participant information sheet.

8.1.2 Prospective cohort

All men with localised prostate cancer diagnosis made at the hospital or referred to the hospital or Prof Mark Emberton's private practice will be identified prior to the man having made a treatment decision but at least one week after the initial clinic appointment in which the diagnosis was given. Patients will be identified through the multidisciplinary team meeting, in clinic and from theatre lists. The participant information sheet will then be given or sent to men if they are interested.

8.1.3 Compensation

Patients agreeing to take part in the study and completing the interviews will receive compensation in the form of £40 gift vouchers.

9 STATISTICAL METHODS

The present study will use qualitative research methods.

The sample size was determined based on the review of the existing literature on qualitative research in prostate cancer and discussions with a qualitative researcher.

An interview guide will be defined for all semi-structured interviews, with the input of the andrologist and qualitative researcher, part of the study team.

Upon consent, follow-up phone calls will be performed if new themes arise from the first interviews and result in an amendment of the interview guide.

The interpretation and analysis of data from the qualitative part of the study will be conducted with a qualitative researcher, member of the study team, manually and with the help of a designated software (NVivo version 12). An exploratory thematic analysis will be performed to find recurrent themes that will be grouped into clusters of experiences. We will then be able to find clusters of agreement and disagreement, that will be illustrated by selected patients' quotations. Each transcript will be analysed separately by two researchers of the study team and every disagreement will be solved by consulting with a third member of the team.

Research will be conducted and reported according to the Consolidated criteria for reporting qualitative research (COREQ) statement [15].

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Although no formal patient and public involvement is planned in this study, we expect that future patients will benefit from the results obtained. The retrospective cohort will help explore and define the most important components in men undergoing focal therapy. The prospective cohort will help find domains with a greater decrease in performance. These results will improve the information given to patients before treatment at the difficult time of decision-making.

Patients will be given the possibility to receive and give their opinion about the transcripts obtained from their interviews, the analysis, and the final results of the study.

11 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH.

The salary of the chief investigator is provided for the duration of the study through a grant from the Fondation de France, and a scholarship from the European Urology Scholarship Program. The research costs for the study will be supported by industrial funding from Angiodynamics.

The Chief Investigator or collaborators report no direct personal involvement in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest.

12 DATA HANDLING AND MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCL is the data controller; the UCL Data Protection Officer is data-protection@ucl.ac.uk . The data processors are UCLH, London Urology Specialists and HW secretarial services. The study will be collecting the following personal data: full name, date of birth, patient number, age, employment

status, ethnicity, treatment type and date, sexual orientation and detailed sexual function. Patients will be able to withdraw their data up to 4 weeks after the interview. Data will not be available to any commercial organisation but remain the responsibility of the researcher undertaking the study. Patients will be able to withdraw from the study at any time and data collected up to that point will be deleted unless agreed otherwise.

A data flow diagram is presented in Figure 3.

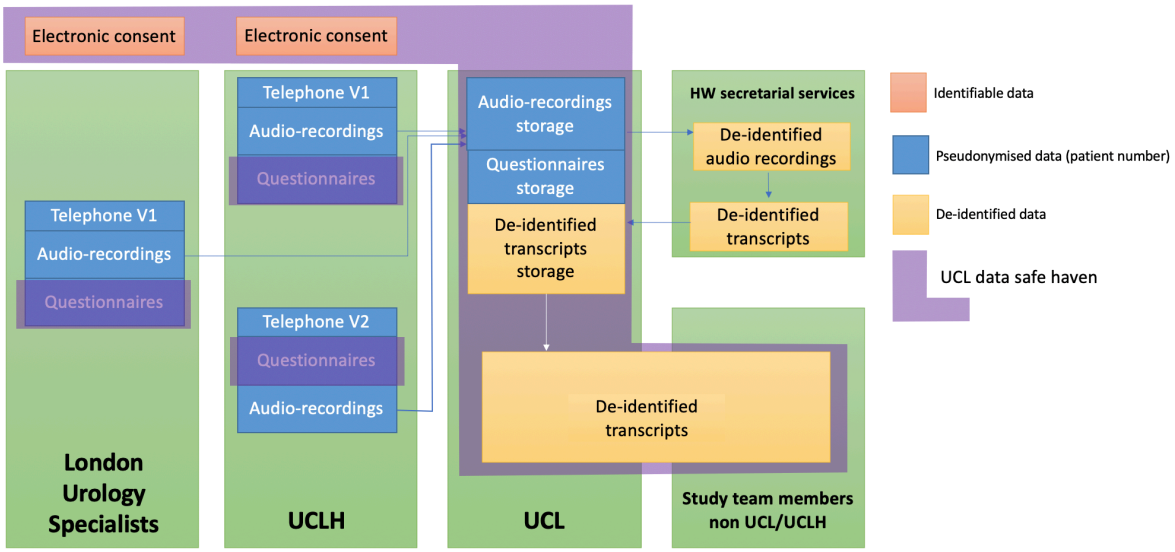


Figure 3. Data flow diagram

<u>Flow of data/retrospective part (of note, the CI=researcher is also a physician and holds a UCLH honorary contract)</u>

- Extraction list of patients treated by IRE in the past 24 Months (secretary of the physician in care of the patients)
- Invitation letters sent (secretary of the physician in care of the patients)
- PIS sent (research team/secretary)
- Contact made with patients agreeing to be contacted to obtain consent and arrange for interview (research team)
- Electronic consent using REDCap in UCL Data Safe Haven + storage
- Attribution of a patient number (using a random number generator)
- Questionnaires administered by email using REDCap in UCL Data Safe Haven + storage
- Interview (researcher): using patient number
- Patient number used for the collection of socio-demographic data (age, ethnicity, employment, sexual orientation, date of treatment)

- Recording of qualitative interview identified by patient number. Number will be removed for complete de-identification before sending recordings for external transcription. Interview transcripts will be de-identified.
- The list containing patients' names and numbers will be kept in UCL Data Safe Haven.
- De-identified recordings and transcripts will be saved in a UCL password-protected computer ('S' drive) and UCL safe haven.

Flow of data/prospective part (of note, the CI=researcher is also a physician and holds a UCLH honorary contract)

- Invitation to take part in the study and PIS delivery (physician in care of the patients)
- Contact made with patients agreeing to be contacted to obtain consent and arrange for interview (research team)
- Electronic consent using REDCap in UCL Data Safe Haven + storage
- Attribution of a patient number (using a random number generator)
- Questionnaires administered by email using REDCap in UCL Data Safe Haven + storage
- Interview (researcher): using patient number
- Patient number used for the collection of socio-demographic data (age, ethnicity, employment, sexual orientation, date of treatment) and questionnaires
- Recording of qualitative interview identified by patient number. Number will be removed for complete de-identification before sending recordings for external transcription. Interview transcripts will be de-identified.
- The list containing patients' names and numbers will be kept in UCL Data Safe Haven.
- De-identified recordings and transcripts will be saved in a UCL password-protected computer ('S' drive) and UCL safe haven.

Once the interview will be conducted a unique ID will be assigned and data will be de-identified and prior to transcription and sharing with the research team. Data will be stored on UCL data safe haven.

The records will be kept digitally with access available to named individuals from the study group only. Medical data will be stored in the electronic medical record of each patient accessible using the EPIC software. Audio recordings (UCL) and transcripts will be kept as digital files and also saved in the UCL data safe haven. Access will be password protected. For digital storage and data transfer, the safe haven and transfer solutions provided by UCL will be used. Recordings will be used for training, quality control, audit and specific research purposes.

The data will be retained for a minimum of 20 years after the end of the study. Any information which leaves the hospital will be anonymised. The Investigator is ready to receive and cooperate with any auditor designated by the Sponsor to ascertain the performance of the study according to Research Governance. The Investigator will retain originals of the approved project protocol,

patients' participation agreements, relevant source documents (patient questionnaires and protocol files, protocol documents) and all other supporting documentation related to the project. He will make these files available for inspection by an authorized representative of the Sponsor or the regulatory authorities upon reasonable request. All study-related records, including source documents, case report forms, and regulatory documents, will be retained for at least 20 years after the end of the study. These documents should be retained for a longer period if demanded by regulatory requirements or by an agreement with the Sponsor. All electronic hardware and records will be heavily encrypted. No data will be transferred outside the UK.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCL

- The Sponsor considers the procedure for obtaining funding from European Urology Scholarship Program to be of sufficient rigour and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences.

14 ASSESMENT AND MANAGEMENT OF RISK

Risks for patients:

Ethical issues:
Protecting patients' anonymity will be of the utmost importance. All recordings and transcripts will be anonymised to prevent from tracing back to patient's identity (de-identified). Only key demographic features will be recorded.

Distress and discomfort from talking about sensitive issues with an unknown researcher: to minimise the risks, all patients will be willing to discuss these issues before entering the study. Extra care will be taken in the design of the introduction and interview prompt, as well as training of the researcher before the first interviews. Interview transcripts will be analysed after a pilot phase (5 patients) to ensure comfort and appropriateness of the interviews

A very low added risk for adverse events is expected from this study with the administration of questionnaires.
A mechanism for reporting adverse events which occur between signing consent and the interview, or filling in the questionnaire, will be in place.

In case of unexpected findings related to the patient's health, the GP will be contacted for further action.

Risks for researchers:

Discomfort discussing sensitive issues with patients. To prevent this, adequate training will be obtained before beginning the interviews.

15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

15.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

15.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

15.2.1 Severity

The generic categories below are given for use as a guide.

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

15.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the study is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this study to capture events related to the surgery. The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the study.

The differentiated causality assessments will be captured in the study specific CRF/AE Log and SAE form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).

Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

15.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure listed in the Investigator Brochure, SPC, manual of Operation **or clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the procedure listed in the manual of operation **or clearly defined in this protocol.**

* this includes listed events that are more frequently reported or more severe than previously reported

15.3 Recording adverse events

All adverse events will be recorded in the medical records in the first instance.

All Adverse events will be recorded in the CRF following consent.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded in the CRF until the participant completes the study.

15.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log.

All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI or another member of the study team will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

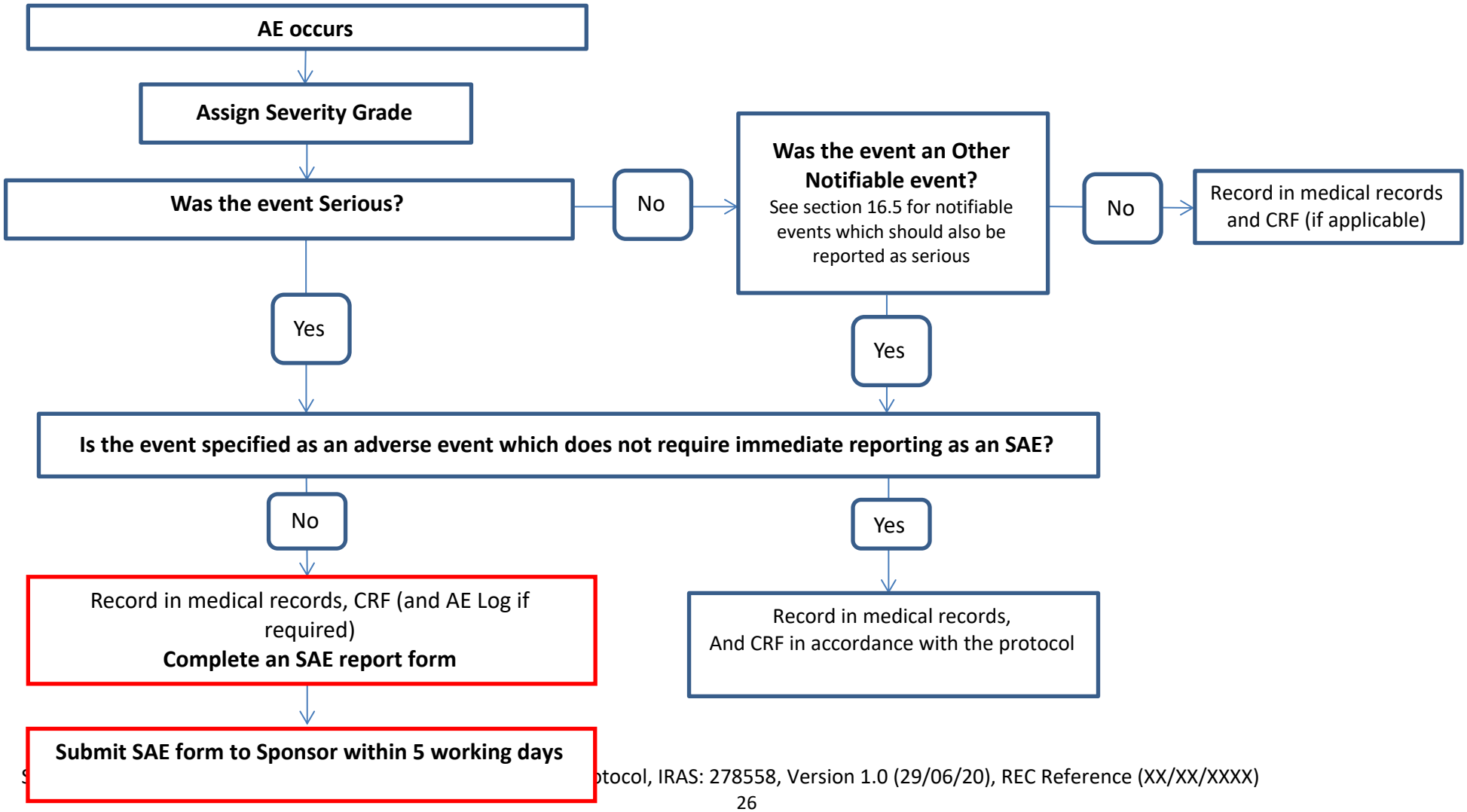
Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor

Email forms to

Research-incidents@ucl.ac.uk

Flow Chart for SAE reporting



15.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

15.6 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

15.9 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

16 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study including herself. Appropriate training records will be maintained in the study files. Training will include Good Clinical Practice, GDPR, Data Protection Act, Information Governance, information Security and EPIC research add-on training. Training for the CI will be performed using online validated learning portals (UCL, UCLH, MRC, NIHR) and the CI will ensure recording of other sources of training for members of the study team.

18 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL. With the understanding that they may use know-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCL IPR.

1. All background intellectual property rights (including licences) and know how and their improvements used in connection with the Study shall remain the property of the Party introducing the same and the exercise of such rights for purposes of the Study shall not knowingly infringe any third party's rights.
2. All intellectual property rights and know how in the Protocol, and in the study data, excluding clinical procedures developed or used by the Participating NHS / HSC Organisation independently of the Study, shall belong to the Sponsor. The Participating NHS / HSC Organisation hereby assigns all such intellectual property rights, and undertakes to disclose all such know how, to the Sponsor.
3. Subject to clauses 1 and 2, all intellectual property rights deriving or arising from the Material or any derivations of the Material provided to the Sponsor by the Participating NHS / HSC Organisation shall belong to the Sponsor.
4. At any time within the duration of the Study, the Participating NHS / HSC Organisation shall at the request and expense of the Sponsor execute all such documents and do all acts necessary to fully vest the intellectual property rights in the Sponsor. To give effect to this clause 4, the Participating NHS / HSC Organisation shall ensure that its agents involved in the Study assign such intellectual property rights falling within clauses 2 and 3 and disclose such know how to the Participating NHS / HSC Organisation.
5. Subject to this Clause 5 and Clause 6, nothing in this Appendix shall be construed so as to prevent or hinder the Participating NHS / HSC Organisation from using its own know how or clinical data gained during the performance of the Study, at its own risk, in the furtherance of its normal activities of providing clinical care to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of the Sponsor, or their funder. This clause 5 does not permit the disclosure of any of the study data, all of which remain

confidential until publication of the results. Any study data not so published remains the confidential information of the Sponsor, or their funder.

6. The Participating NHS / HSC Organisation may, with the prior written permission of the Sponsor (such permission not to be unreasonably withheld), use study data gained during the performance of the Study, at its own risk, in the furtherance of its normal activities of commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of the Sponsor or their funder. This clause 6 does not permit the disclosure of any of the study data, all of which remain confidential until publication of the results of the Study.

19 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

20 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that she will archive the study master file in the UCL Data Safe Haven for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for 20 years and in line with all relevant legal and statutory requirements.

21 PUBLICATION AND DISSEMINATION POLICY

The results of the present study will be published and presented during UK and international conferences. At least two articles and two conference presentations will be expected from the present study. Authorship will be granted to all members of the study team. The first author will be the person who contributed most to the work, including writing of the manuscript. The sequence of authors will then be determined by the relative overall contribution to the work and the manuscript. The last author will be in charge of supervising the study team, making final changes and final validation of the manuscript. No article or abstract should be submitted without the validation of all members of the study team. A short report will be sent to participants who asked for it.

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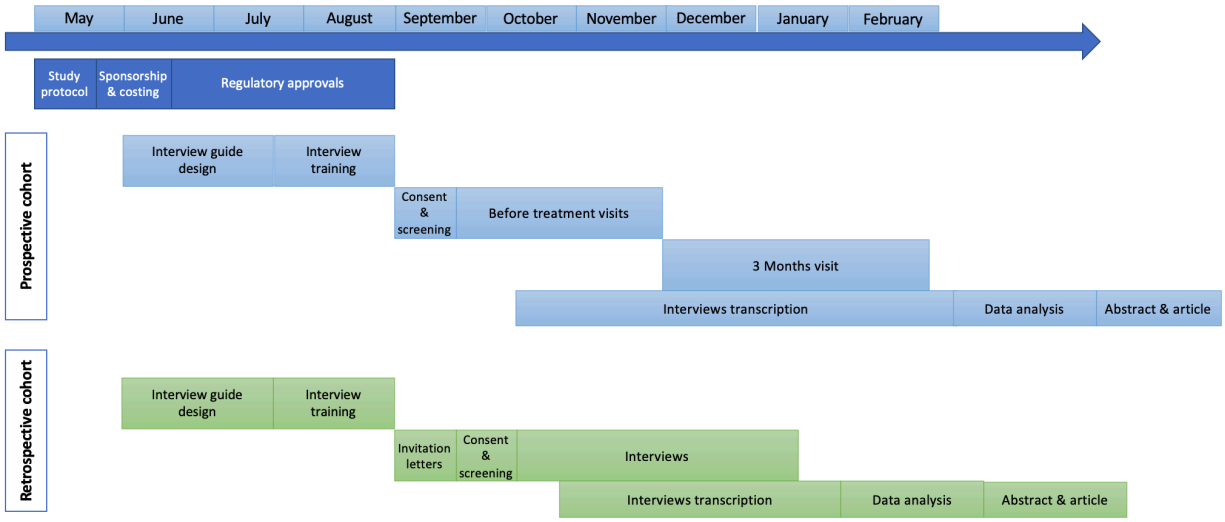
23 APPENDICES

23.1 Study timeline



23.2 Study visits

Retrospective cohort	V0 Inclusion	V1
Eligibility criteria	✓	
Information note	✓	
Electronic consent	✓	
Questionnaires		✓
Telephone interview		✓

Prospective cohort	V0 Inclusion	V1 Before treatment	V2 3 Months
Eligibility criteria	✓		
Information note	✓		
Electronic consent	✓		
Questionnaires		✓	✓
Telephone interview		✓	✓

23.3 Questionnaires

- IIEF-15
- MSHQ-EJD-SF

23.4 Participant information sheets

- Retrospective cohort
  Prospective cohort

23.5 Participant Informed Consent Form