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Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods

Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men

Protocol: "UPSTREAM - Phase II" Further Follow Up Study

Version 1.0, 21/10/2019

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Preface

The UPSTREAM project (NIHR HTA reference 12/140/01) conducted a pragmatic, two-arm, multicentre, randomised controlled trial (RCT) to determine the clinical and cost-effectiveness of invasive urodynamics for the diagnosis and management of bladder outlet obstruction (BOO) in men. Men from 26 urology departments of NHS Hospitals in England who had bothersome lower urinary tract symptoms (LUTS) and were seeking further treatment, which may have included surgery, were randomised to one of two study arms; 'Routine Care' (as per the NICE diagnostic pathway[1]), or routine care plus invasive urodynamics ('Urodynamics'), which is currently optional. The design was utilised to establish noninferiority in symptom severity (International Prostate Symptom Score [IPSS]) 18-months post-randomisation. The primary outcome was IPSS at 18-months post-randomisation, and a key secondary outcome was the influence of urodynamics (UDS) on rates of bladder outlet surgery. The RCT started 01 April 2014 and ended 30 September 2018. The trial protocol and statistical analysis plan (SAP) are published elsewhere.[2,3]

In 2018, for reasons alluded to in *this* protocol (below), the NIHR HTA awarded a funding extension to conduct further (long term) follow up of UPSTREAM participants, five years post-randomisation. The further follow up phase started 01 July 2019 with a planned end date of 30 June 2022 and details of the work are presented in this protocol.

Thus, for the purpose of clarity, the RCT conducted between 2014 and 2018 is referred to as "UPSTREAM - Phase I"[2,3] and the additional follow up at five years post-randomisation, as "UPSTREAM - Phase II".

Study Management Group

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**We wish to acknowledge Professor Rob Pickard, a Consultant Urological Surgeon and co-applicant, who sadly passed away in July 2018. Professor Pickard was a major contributor in developing the original funding application and contributed valuable expertise to study design and oversight of UPSTREAM - Phase I.*

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This protocol describes the **"UPSTREAM - Phase II" Further Follow Up Study** and provides information about procedures. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to those involved with delivering the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will be conducted in accordance with the UK Policy Framework for Health and Social Care, International Conference on Harmonisation Good Clinical Practice (ICG-GCP), the Data Protection Act, General Data Protection Regulation (GDPR) and other regulatory requirements, as appropriate.

Study Summary

Title:	UPSTREAM *(Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods)* Phase II – Further Follow Up Study.
Acronym:	UPSTREAM - Phase II.
Design:	Further follow up (five years post-randomisation) of the UPSTREAM randomised controlled trial (RCT).
Population:	Existing participants of the UPSTREAM RCT (UPSTREAM - Phase I).
Aims:	The aim of this second phase of the UPSTREAM project (UPSTREAM - Phase II) is to undertake the longer term follow up of UPSTREAM participants at five years post-randomisation. We aim to identify: the symptom outcomes of treatment; definitive surgery rates in the two study arms; and the long-term impact of lower urinary tract symptoms (LUTS) and its therapy. The focus will continue to be on effectiveness and patient outcomes as per the original commissioning brief.

Outcomes and measures:	• LUTS will be measured with the widely-used patient reported outcome, the International Prostate Symptom Score (IPSS), at five years post-randomisation.
	• Measures from the International Consultation on Incontinence Questionnaires (ICIQ) will also be used, giving sensitive and comprehensive assessment of LUTS severity/ bother, sexual function and quality of life (QoL), i.e.:
	  ○ IPSS QoL
	  ○ ICIQ Male LUTS (ICIQ-MLUTS)
	  ○ ICIQ sexual function in Male LUTS (ICIQ-MLUTS-sex)
	• The EQ-5D-5L will be used to provide the QoL weights used to calculate Quality Adjusted Life Years (QALYs).
	• Data for: Surgery rates (the relative proportion of men in each group having surgery up to five years post-randomisation); diagnostic testing after the main trial (where possible); and resource use will be obtained via a one-off bespoke data extraction of Health Episode Statistics (HES) and HES-Office of National Statistics (ONS) linked data, via NHS Digital. This will include individual level data about participants' relevant: inpatient stays; outpatient attendances: including procedures; radiology and accident and emergency (A&E) episodes; and cause of death (where applicable).

Sponsor:	North Bristol NHS Trust (reference number: R&I 4560)
Co-ordination:	*Central:* by Chief Investigator (Lead Urologist) and Study Office in Bristol. *Overall:* by the Project Management Group and overseen by the Trial Steering Committee.
Funding:	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 12/140/01).
Ethics committee details:	South Central – Berkshire (reference: 19/SC/0578; approval 01 November 2019)
ISRCTN:	ISRCTN56164274
Key dates:	*Start date:* 1 July 2019 (for 36 months) | *Planned end date:* 30 June 2022 | *Planned reporting date:* July 2022

Contents

Glossary of abbreviations

AE	Adverse Event
BAUS	British Association of Urological Surgeons
BOO	Bladder outlet obstruction
BPO	Benign prostatic obstruction
BRTC	Bristol Randomised Trials Collaboration
BTC	Bristol Trials Centre
CI	Chief Investigator
CRF	Case report forms
DMC	Data Monitoring Committee
EAU	European Association of Urology
EQ-5D-5L	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HES	Hospital Episodes Statistics
HTA	Health Technology Assessment
ICIQ-MLUTS	International Consultation on Incontinence Questionnaire – Male Lower Urinary Tract Symptoms
ICIQ-MLUTSsex	International Consultation on Incontinence Questionnaire – Sexual Matters associated with Male Lower Urinary Tract Symptoms
IPSS	International prostate symptom score
ISRCTN	International Standard Randomised Controlled Trial Number
LUTS	Lower urinary tract symptoms
NBT	North Bristol NHS Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
PMG	Project Management Group
PP	Patient Panel
PROs / PROMs	Patient reported outcomes / Patient reported outcome measures

QALY	Quality adjusted life years
RCT	Randomised controlled trial
R&D	Research and Development
R&I	Research and Innovation
SD	Standard deviation
SAE	Serious Adverse Event
TSC	Trial Steering Committee
TURP	Transurethral resection of prostate
UK	United Kingdom
UDS	Urodynamic studies

Keywords

Benign prostatic obstruction, Bladder outlet obstruction, Cost-benefit analysis, Detrusor overactivity, Detrusor underactivity, Diagnostic tests (routine), Lower urinary tract symptoms, Patient reported outcome measures, Prostate, Randomised controlled trial, Surgery, Underactive bladder, UPSTREAM, Urinary bladder neck obstruction, Urinary retention, Urodynamics, Urologic surgical procedures.

Flow Diagram

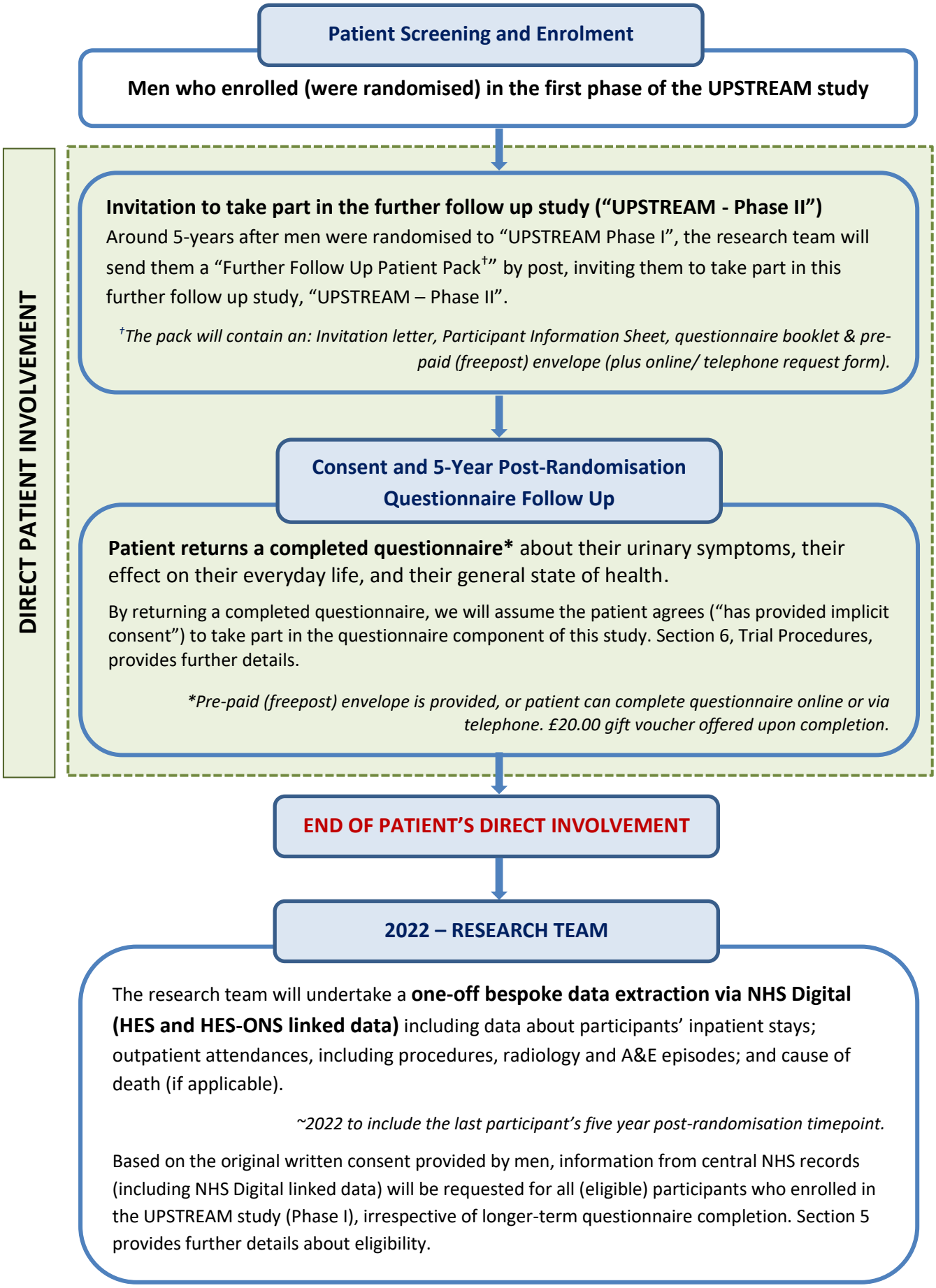

Figure 1 **UPSTREAM Phase II – Further Follow Up Study**

1. Introduction

This protocol describes Phase II of the UPSTREAM project, the "Further Follow Up Study". Phase I of the project comprised a major multicentre UK trial, "the UPSTREAM trial" that is detailed in a separate protocol (Protocol, version 4, 29 September 2016). Full details, including study 'Background' are provided in the protocol for Phase I, which is also published.[2]

1.1. Title

"UPSTREAM - Phase II" Further Follow Up Study. ***(Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM)).***

1.2. Background

In brief, lower urinary tract symptoms (LUTS) are a common feature of ageing.[4] They can be categorised as problems with voiding (passing urine) or storing urine. In men with voiding LUTS, benign prostate enlargement (BPE) with ageing causes benign prostatic obstruction (BPO). For such patients, prostate surgery, such as transurethral resection of the prostate (TURP), may improve LUTS. However, voiding LUTS can also be caused by bladder dysfunction: e.g. poor expulsion strength of the bladder muscle, called 'detrusor underactivity' (DU). In such men, it is hard to justify prostate surgery if BPO is not present, especially in view of potential adverse effects.

The UPSTREAM trial (Phase I) evaluated the assessment of lower urinary tract symptoms (LUTS) in men who were seeking further treatment for their bothersome LUTS, which may have included surgical intervention.[2] Men were randomised to a care pathway which included or omitted invasive urodynamic (UDS) testing (Urodynamics arm [intervention] and Routine Care arm [control]). Following assessments, men decided their therapy in discussion with their healthcare professional, which could have been conservative (advice, medication) or interventional (procedures to relieve BPO). The primary outcome was the patient-reported International Prostate Symptom Score (IPSS) at 18-months post-randomisation, and a key secondary outcome was rates of bladder outlet surgery. Study recruitment was from October 2014 to December 2016, and the trial ended September 2018; details are published elsewhere.[2,3] The baseline characteristics and initial diagnostic testing outcomes for the trial are published,[5] as is qualitative evidence regarding the attitudes to, and experience of, UDS testing from men at each end of the clinical pathway.[6] We expect to publish the results of main outcomes, including health economics and additional qualitative findings, in 2019/2020.

To recap, the objectives of the UPSTREAM trial (Phase I) were to answer the following questions:

1) Does invasive urodynamics deliver similar or better symptomatic outcomes for LUTS measured by IPSS at 18-months after randomisation?
2) Does invasive urodynamics influence surgical decision-making, as reflected in differing surgery rates in the two diagnostic pathways?
3) What is the cost effectiveness of the two diagnostic pathways (quality-adjusted life-year (QALY) gained at 18-months post randomisation)?
4) What are the relative harms of invasive urodynamic tests, and surgical and conservative management?

5) What subsequent NHS services are required (including repeat surgery or catheterisation for acute urinary retention) for men in each arm?
6) What are the differential effects on other outcomes, such as quality of life and general health?

Implicit is the recognition that we anticipated that there would probably be different surgery rates in the two arms. Men reporting voiding LUTS undergoing UDS would have the underlying mechanism identified (BPO or DU), and those men with DU would not be recommended for surgery. In the non-UDS arm (Routine Care), there would be an assumption of BPO as the mechanism (even though in reality a proportion would actually have DU). Consequently, a higher surgery rate would be anticipated in the non-UDS (Routine Care arm). This difference means that identification of all men proceeding to surgery is important, specifically for objectives #2-5, listed above.

The nature of clinical delivery in the National Health Service (NHS) means that patient pathways for benign conditions can be protracted. For male LUTS, during the UPSTREAM trial (Phase I), we experienced a situation whereby diagnostic tests added considerable duration to the overall pathway. Being an extra test, people in the intervention (Urodynamics) arm generally had longer to wait than those in the non-UDS (Routine Care) arm. In many cases, the assessment was a substantial proportion of the 18-months trial duration. Hence, surgery may have taken place in the recent past at 18-months (too close for full recovery from surgery). In some cases, the assessments took longer than 18-months, so the surgery rates at 18-months may not fully reflect the decisions finally taken by doctors and patients. The Urodynamic arm is at greater risk of being affected by these in both cases.

In the medium term, patients managed conservatively may re-present since they are likely to experience ongoing symptomatic bother from LUTS. Each time, the consultation may result in a decision to proceed to additional investigation and potentially undergo surgery. Consequently, a longer-term appreciation of the assessment and therapy may identify a move away from the initial decision.

The proposal for this second phase of the UPSTREAM project (Phase II "Further Follow Up") is to undertake the follow up of UPSTREAM participants at five years post-randomisation, aiming to identify;

1) definitive surgery rates in the two arms;
2) symptom outcomes of treatment, allowing enough time for full recovery from surgery; and
3) the long-term impacts of LUTS and its therapy.

The focus will continue to be on effectiveness and patient outcomes as in the original commissioning brief. Full details of the Aims and Objectives can be seen in Section 2, below; in brief, we propose assessing up to five years post-randomisation:

1) patient reported urinary primary outcomes *(PROMs questionnaires; IPSS, ICIQ-MLUTS and ICIQ-MLUTS-sex)*;
2) rates of surgery *(via NHS Digital)*;
3) quality adjusted life years (QALYs) *(EQ-5D-5L)*;
4) resource use for LUTS diagnostic tests and therapy *(via NHS Digital, where possible)*; and
5) cost-effectiveness from an NHS secondary care perspective *(via NHS Digital)*.

1.3.Rationale for "UPSTREAM - Phase II" Further Follow Up Study

There are three principal advantages to the completion of the further follow up study:

1) Confident identification of the complete surgery rates in both study arms, overcoming the potential incomplete data for the Urodynamics arm due to the greater duration needed to complete all diagnostic assessments;
2) Proper identification of the symptomatic outcomes, avoiding the detrimental effect for those men whose primary outcome of Phase I (i.e. IPSS at 18-months post-randomisation) was captured during the recovery window of surgery (likely to affect the Urodynamic arm more than the non-UDS, Routine Care arm); and
3) Evaluation of the resource use and health economic implications in the long-term; this will be a crucial differential if surgery rates are different between the two arms.

The clinical pathway in the main trial (UPSTREAM - Phase I) proved longer than expected, such that some patients listed for surgery did not receive it by the end of their participation in the trial, or underwent surgery close to the 18-month follow up. This was an unexpected problem, representing failure to comply with NHS referral-to-treatment targets, which worsened during the trial. This is potentially a fundamental issue, as the trial is predicated on differential surgery rates between the two arms (we hypothesised that the Urodynamics intervention arm would be non-inferior for symptoms, but at a lower surgery rate). Thus, we need scrupulous surgery data to be able to report whether surgery rates were indeed lower.

Following completion of the main trial (UPSTREAM - Phase I), the men with persisting voiding symptoms managed conservatively may subsequently have received surgery (with a surgical recommendation based on "in case symptoms improve"/ "nothing else to offer") in the ensuing years. This further follow up (UPSTREAM - Phase II) would address this issue, which would be a definite step to maximising impact, avoiding the "doing the operation anyway, regardless of assessment" mentality sometimes encountered in clinical practice.

LUTS are complex and it is recognised that:

- they are potentially a long-term problem;
- prone to manifest a placebo response, including with surgery; and
- they respond differentially to treatment (most importantly that storage LUTS, such as urgency and nocturia, are less likely to respond to surgery relieving BOO than voiding LUTS are).

Thus, this long-term further follow up will help understanding of the sustained response, placebo impact and the behaviour of storage LUTS over time. This further follow up will help us to state for sure whether or not UDS delivered non-inferior symptom outcomes with lower surgery rates. Furthermore, there is very little information documented about men's attitudes to the long-term experience on LUTS and its treatments, and the European Association of Urology (EAU) has identified this as a priority research need.[7]

1.4.Additional insights

In addition to above, this further follow up will give extra information in relation to influences on good or a bad outcome. Some examples of the potential influences on outcome include:

1) Men who are bothered by a slow stream and other voiding LUTS caused by prostate enlargement should have a significant improvement with successful surgery to relieve BOO. However, only urodynamic testing can decide if BOO is actually present; if it was not included in the diagnostic pathway, the clinician has to rely on indirect assessments to surmise whether BOO is likely to be present.

2) Nocturia is one of the main drivers for a man to present for urological assessment and potentially reflects a range of medical and other influences. The symptom is comparatively unlikely to improve with surgery to relieve BOO, but anecdotally some men appear to experience improved nocturia after prostate surgery.

3) Urgency is another main driver for review; some doctors think urgency may be secondary to BOO, while others consider it as principally due to bladder dysfunction.

4) Post micturition dribble is a particular nuisance symptom which affects many men to a considerable extent, despite the comparative modest volume of urine involved.

Understanding how men can anticipate long term change in these key symptoms according to their assessments and interventions will be a very interesting element of this five year follow up.

2. Study Aims and Objectives and Outcome Measures

To recap, the aim of the UPSTREAM trial (Phase I) was to determine whether a care pathway including UDS (Urodynamics arm) was no worse for men, in terms of symptom outcomes, than one in which it was not included (Routine Care) at 18-months post-randomisation.[2,3] The primary clinical outcome was measured with the widely-used patient reported outcome measure (PROM), the IPSS, at 18-months post-randomisation. A key secondary outcome was to also establish whether inclusion of invasive UDS reduced rates of bladder outlet surgery; surgical rates within 18-months of randomisation were obtained via case report forms (CRFs) completed by trained hospital staff.

It was established during the UPSTREAM trial (Phase I) that there is considerable variability in the diagnostic pathway, including duration, across 26 secondary care sites across England, as well as in patient factors. We identified that several patients had not fully completed their LUTS therapy at the time of the primary outcome assessment (18-months post-randomisation) or had completed it less than six-months beforehand. Clinically this is an insufficient timeframe to offer full insight into impacts of surgical interventions. Thus, the key aim of this further follow up (UPSTREAM - Phase II) is to establish the long term primary outcome response, i.e. five years post-randomisation, compared between arms.

2.1.Aim

To determine intervention rates and outcomes in UPSTREAM participants at five years post-randomisation.

2.2.Objectives

To answer the following questions at five years post-randomisation:

A) What are the symptomatic outcomes for LUTS, measured by the IPSS?

B) What are the surgery rates in the two diagnostic pathways (the relative proportion of men having surgery)?

C) Was additional diagnostic testing (e.g. UDS) undertaken after the completion of UPSTREAM - Phase I? *(where possible)*

D) What are the differential effects on other outcomes, such as symptom: severity and bother; sexual function; quality of life (QoL); and general health?

E) What is the cost effectiveness from an NHS secondary care perspective using the QALY as the economic outcome?

F) What is the differential use of NHS resources?

2.3. Outcomes

- LUTS five years post-randomisation, measured with the IPSS, PROM (objective A). The IPSS is validated,[8] well-known and widely used in the NHS.
- Alongside the IPSS (including the QoL measure), measures from selected International Consultation on Incontinence Questionnaires (ICIQs) will be used, collectively giving sensitive and comprehensive

assessment of QoL, LUTS severity/ bother, sexual function, and general health (objective D). The following measures will be used:

  - IPSS – including QoL;
  - ICIQ Male LUTS (ICIQ-MLUTS^); and
  - ICIQ sexual function in Male LUTS (ICIQ-MLUTS-sex^).

  ^Copies of ICIQ materials can be requested from http://iciq.net

- The EQ-5D-5L will be used to provide the QoL weights used to calculate QALYs (objective E).
- Data for objectives 'B' (surgery rates), 'C' (diagnostic testing), and 'F' (resource use) will be obtained via a one-off bespoke data extraction of Health Episode Statistics (HES) and HES-Office of National Statistics (ONS) linked data via NHS Digital. See Section 2.4.2 for further details.

2.4.Outcome measures

The components and timing of follow up measures are shown in Table 1.

2.4.1 PROMS

PROMs (standardised questionnaires) will form the "5-year follow up" questionnaire booklet, which will be completed at each participant's five years post-randomisation timepoint, or thereabouts (objectives A, D and E). Participants will be able to complete the questionnaire booklet via post, online or telephone, as detailed in Section 6, Trial Procedures.

2.4.2 Data extraction via NHS Digital

To assess surgery rates, whether additional diagnostic testing was undertaken after the completion of UPSTREAM - Phase I (where possible), and resource use (objectives B, C and F) we will utilise individual level data obtained via a bespoke data extraction of HES and HES-ONS linked data, via NHS Digital. The data extraction will include individual level data about participants' relevant: inpatient stays; outpatient attendances: including procedures; radiology and accident and emergency (A&E) episodes; and cause of death (where applicable).

We envisage the extraction taking place in 2022 to (ideally) include the last participant's five year post-randomisation timepoint. The exact date of extraction, however, will be decided in collaboration with NHS Digital to maximise data collection. We may conduct an earlier extraction to inform the data analysis; this will be decided as the trial progresses.

Table 1 **Measurement outcomes table: components/ timing**

	5-years post-randomisation[a]	2022[b]
Patient reported outcome measures (PROMs)		
IPSS (including QoL)	●	n/a
EQ-5D-5L	●	n/a
ICIQ-MLUTS	●	n/a
ICIQ-MLUTS-sex	●	n/a
Individual level data extraction via NHS Digital undertaken by the research team		
NHS Digital (HES and HES-ONS; inpatient stays; outpatient attendances: including procedures; radiology and accident and emergency (A&E) episodes; and cause of death, where applicable).	n/a	◊

[a] *Each UPSTREAM participant will be followed-up as close as possible to their five years post-randomisation timepoint. Given the long-term nature of this further follow up, however, data from 4-years to 6-years post randomisation will be accepted. Available data outside this range will be reviewed and considered by the Trial Statisticians and Trial Steering Committee (TSC).*

[b] *We envisage a one-off data extraction of HES and HES-ONS linked data (NHS Digital) will take place in early 2022 to include the last participant's five year post-randomisation timepoint. The exact date of extraction, however, will be decided in collaboration with NHS Digital to maximise data collection within the available grant timeframe. We may conduct an earlier extraction to inform the data analysis; this will be decided as the trial progresses.*

Key:

● PROMs will be available for participants to complete via post, online, or telephone; alternative methods of completion are offered to minimise loss to follow up. Reminder letters and phone calls will also be used where appropriate, and if necessary, we will offer a shortened version of the questionnaire booklet to ensure that critical data (i.e. the IPSS and EQ-5D-5L as a minimum) are obtained.

◊ NHS Digital bespoke data extraction undertaken by the research team.

3. Study Design

Further follow up of the UPSTREAM randomised controlled parallel-group trial, at five years post-randomisation.

4. Setting

For Phase I of the UPSTREAM project, Urology departments of at least 26 NHS Hospitals in England were responsible for the recruitment, assessment and treatment of UPSTREAM; see details published elsewhere.[2]

For the purpose of this further follow up (UPSTREAM - Phase II), no clinical assessments are proposed, rather data collection is via PROMS (questionnaires) and data extraction via central NHS records (e.g. NHS Digital linked data). Thus, it is not necessary for men to return to their local Hospital, nor will they (or the coordinating research team) require contact with their Urology clinical care team.

The central (coordinating) research team based at the Bristol Randomised Trials Collaboration (BRTC), as part of the Bristol Trials Centre (BTC), will be responsible for coordinating and delivering the study components. North Bristol NHS Trust will have oversight of data collection and responsibility for reporting through the NIHR. Trial Procedures are detailed in Section 6, below.

5. Eligibility Criteria

5.1.Population

Existing participants of the UPSTREAM trial (UPSTREAM - Phase I).

> ***NB**: the research team will only approach men who were randomised (enrolled) to the UPSTREAM trial (Phase I); new patients (men) who are seeking treatment for their bothersome LUTS are <u>not</u> being recruited.*

Inclusion/exclusion criteria for this further follow up study (UPSTREAM - Phase II) differs between the 'PROM' (questionnaire) component and the 'NHS Digital data extraction' component. To summarise why; *all* men who enrolled in the UPSTREAM trial (Phase I) provided written informed consent, which included the essential statement *"I agree that information relevant to the UPSTREAM study may be collected from my hospital and NHS records, including Office of National Statistics (ONS), NHS central registers and the Health and Social Care Information Centre, and that this data may be used to follow my ongoing health after the study"*. Thus, additional ('new') consent is not required to request data via NHS Digital for the purpose of this study. The statement *"I am willing to be contacted in the future for long-term follow-up",* however, was optional. These differences influence trial procedures, so the inclusion and exclusion criteria for each component are outlined below for clarity. Trial Procedures for each component are then detailed in Section 6.

5.2. PROMS (questionnaire) study component

5.2.1 Inclusion criteria

Men randomised (enrolled) to the UPSTREAM trial (Phase I) who were willing to be contacted for long term follow up, as indicated on their original (Phase I) consent form.

5.2.2 Exclusion criteria

Patients who:

- are not already randomised (enrolled) to the UPSTREAM trial (Phase I); and

UPSTREAM (Phase I) participants who:

- are not willing to be contacted about long term follow up;
- have withdrawn trial participation, or at least withdrawn permission to be contacted in the future for long term follow up, at the time of their 18-month timepoint; and/or
- do not consent and/or are not willing or able to comply with essential study procedures of this further follow up (UPSTREAM - Phase II).

5.3. NHS Digital data extraction study component

5.3.1. Inclusion criteria

Men randomised (enrolled) to the UPSTREAM trial (Phase I).

5.3.2. Exclusion criteria

Patients who:

- are not already randomised (enrolled) to the UPSTREAM trial (Phase I); and

UPSTREAM (Phase I) participants who:

- have withdrawn permission for the study to continue to access sections of their medical notes and NHS records, ONS and NHS Central registers information, at the time of their 18-month timepoint.

6. Trial Procedures

6.1.Participant entry: PROMS (questionnaire) study component

The research team will invite participants of the UPSTREAM trial (Phase I) who consented to be contacted for long term follow up and had not amended their relevant permissions at their 18-month (final) follow up, to participate in the questionnaire component of this further follow up study (UPSTREAM - Phase II).

6.1.1. Identification

To identify potential participants, designated member(s) of the research team will review relevant data of the 820 UPSTREAM participants; these data will be extracted from the existing UPSTREAM databases, and manual checking of the UPSTREAM (Phase I) consent forms, withdrawal/change of permission forms and 18-month CRFs, if required.

A three-step process will be undertaken:

i. Review responses to the UPSTREAM (Phase I) consent form statement *"I am willing to be contacted in the future for long-term follow-up".*

Of those who agreed to this optional statement, the research team will then check that the participant did not…:

ii. Withdraw from the study, or change relevant permissions; *nor*
iii. Select the "Not Applicable" response to Section 2.1 of the 18-month CRF completed during Phase I *(i.e. "The patient is willing to be contacted in the future for long-term follow-up" Yes or Not Applicable).*

Men who satisfy the above points ("potential participants") will be invited to take part in the questionnaire component of this follow up study (UPSTREAM - Phase II); see Section 6.1.2, Recruitment and Consent, below.

A member of the research team will complete a study-specific screening log and provide confirmation of the man's outcome for this element of the further follow up study; this is anticipated to be one of four main outcomes: (1) ineligible; (2) eligible and consented to take part; (3) eligible but declined to take part; and (4) potentially eligible but no response to further follow up study invitation - lost to follow up (LTFU). Where possible, screening logs will include reason(s) for non-participation.

6.1.2. Recruitment and Consent

Potential participants will be invited to take part by post, in the first instance. The research team will send men a "Further Follow Up Patient Pack" containing the study invitation letter, Participant Information Sheet (PIS), questionnaire booklet and pre-paid (freepost) return envelope, plus an online/telephone questionnaire request form. Contact details of the trial manager (study office) will be provided in the event of any queries.

Given the 'minor' nature of this questionnaire follow up, we do not propose obtaining additional ('new') written informed consent from men; the burdens are deemed insignificant and sensitive topics are not involved, furthermore, the questions included in the booklet were administered several times to these men during UPSTREAM - Phase I. Instead we will regard the return of the completed questionnaire (paper copy, or completed online or over the telephone), as adequate evidence of consent ("implicit consent"). This approach

fits with NHS Research Ethics Committee (REC) guidance (Integrated Research Application System (IRAS) question A30-2 – Recording consent in writing).[9]

When men originally enrolled in UPSTREAM, their General Practitioner (GP) was informed of their involvement. **Prior to contacting potential participants**, the research team will contact GPs to mitigate any risk relating to them. In the first instance, the research team will contact GPs (practices) with a standard letter (or equivalent email) stating that we intend to contact them in due course regarding the status of a patient to establish that they are alive, have capacity to take part in the study, and still live at the registered address. Before posting the "Further Follow Up Patient Pack" to each potential participant we will then attempt to contact the GP (practice; either by letter/email/telephone) to ascertain the information. If the GP (practice) fails to respond, we will proceed to post the study documents as reasonable attempts to mitigate that risk have been made; this approach is supported by the Sponsor (North Bristol NHS Trust).

If the research team does not receive a response from a potential participant within a reasonable time of sending the "Further Follow Up Patient Pack" (e.g. ~3-4 weeks), then they will try calling the man, and resend another pack with a reminder letter. The research team will make three contact attempts; if no response is received thereafter then we will assume the man is LTFU. A similar model was successfully used during the main trial (UPSTREAM - Phase I). If previous contact with a man's GP (practice), as noted above was unsuccessful then, where feasible, the research team will attempt to contact the GP (practice) again.

All men who agree to take part will be logged with the research team and continue to use the unique 6-digit study (participant) identification number that was allocated in the main trial (UPSTREAM - Phase I). The research team will send a study approved letter to the participant's GP informing them that their patient has agreed to take part in this further follow up (UPSTREAM - Phase II).

6.2.Participant entry: NHS Digital – data extraction study component

6.2.1. Identification and consent

A member of the research team will review relevant data of all 820 UPSTREAM participants; these data will be extracted from the existing UPSTREAM databases, and manual checking of the UPSTREAM (Phase I) consent forms and withdrawal/change of permissions forms, if required.

Specifically, the team will check that the participants did not withdraw permission for the study to continue to access sections of their medical notes and NHS records, ONS and NHS Central registers information, at the time of their 18-month timepoint; data extraction via NHS Digital will only be requested for men meeting this criteria.

As noted above (Section 5.1, Population), men who enrolled in the UPSTREAM trial (Phase I) provided written informed consent, which included the essential statement *"I agree that information relevant to the UPSTREAM study may be collected from my hospital and NHS records, including Office of National Statistics (ONS), NHS central registers and the Health and Social Care Information Centre, and that this data may be used to follow my ongoing health after the study"*.

A member of the research team will complete the study-specific screening log and provide confirmation of the man's outcome, as noted in Section 6.1.1, above.

6.3.Planned interventions and Allocation (randomisation) to trial groups

This protocol refers to the further follow up of existing UPSTREAM participants, specifically at five years post-randomisation (UPSTREAM - Phase II). Thus, no new or subsequent interventions, nor allocation (randomisation) to trial groups, are required. Details of the trial (UPSTREAM - Phase I) interventions and allocation to trial groups are available in the separate protocol (Protocol Phase I, version 4, 29 September 2016), which is also published.[2]

6.4.Blinding

Given the nature of UDS testing and knowledge of results unpinning treatment decisions, group allocation was not concealed from men (nor their clinical care team) during the UPSTREAM trial (Phase I). The trial manager and administrative staff, although unblinded to enable individual data collection, were blinded to aggregate data.

Two statisticians will continue to support this second phase of the UPSTREAM project. The senior statistician (and co-applicant) will remain blinded throughout. A junior statistician will have unblinded access to the data to report outcome data as required. The health economist will be blinded when cleaning data, but unblinded when conducting the analysis. Other members of the study team will remain blinded to aggregate data. The protocol and statistical analysis plan (SAP) will be approved by the Project Management Group (PMG) and Trial Steering Committee (TSC) prior to 'the end of follow up'.

Additional methods/ procedures to protect against bias are discussed in Section 6.6, below.

6.5.Data collection

Outcomes and outcome measures have been previously discussed; see Section 2, including Table 1 *Measurement outcomes table: components/ timing*. To summarise, the further follow up study (UPSTREAM - Phase II) consists of two components: (1) PROMS (questionnaires) and (2) one-off bespoke data extraction of HES and HES-ONS data via NHS Digital.

Eligible men will be invited to complete a study-specific "5-year follow up" questionnaire booklet containing PROMS (i.e. the IPSS, EQ-5D-5L, ICIQ-MLUTs and ICIQ-MLUTS-sex), five years post-randomisation to the UPSTREAM trial (Phase I) *see footnote a*. Return of a completed questionnaire booklet (or at least provision of critical data, such as the IPSS and EQ-5D-5L) marks the end of the participant's direct involvement. Upon receipt of a completed questionnaire booklet (or at least provision of critical data), the research team will offer the participant a £20.00 gift voucher; this is to thank them for completing the final "5-year follow up" questionnaire booklet. Men will also be sent participant newsletters telling them about the study, including progress and results once available, which is expected to be in 2022/2023. Further details about dissemination are outlined in Section 14.

Secondly, additional clinical and resource use data will be collected via a one-off bespoke data extraction of HES and HES-ONS data via NHS Digital. This will include data about participants' relevant: inpatient stays; outpatient attendances: including procedures; radiology and accident and emergency (A&E) episodes; and cause of death (where applicable). We envisage this extraction will take place in 2022 to include the last

participant's five year post-randomisation follow up timepoint[a], although the exact date of extraction will be decided in collaboration with NHS Digital to maximise data collection, within the grant timeframe.

The research team based at the BRTC will be responsible for coordinating and delivering each of the study components.

[a] Given the long-term nature of this further follow up, data from 4-years to 6-years post randomisation will be accepted. Available data outside this range will be reviewed and considered by the Trial Statisticians and TSC.

6.6.Methods/procedures to protect against other sources of bias

6.6.1. Loss to follow up (attrition bias)

We will take active measures to minimise loss of men from the further follow up study in line with ethics approval. This may include, for example:

- reminders to men via various methods (e.g. telephone/ post/ email);
- ability to complete questionnaires (including a short 'essential data' version) via multiple methods (e.g. post/ online/ telephone);
- obtaining back-up 'best contact' addresses;
- contacting their GP (practice) to check their contact details on record are still valid; [10] and
- using vouchers as retention incentives (i.e. men will be offered a £20.00 gift voucher upon receipt of a completed questionnaire).[11]

In addition, we may access centrally-held NHS data (where consent is still in place), for example via the NHS Strategic Tracing Service in England and Wales to find new addresses.

We have extensive experience of using the above strategies and measures, and have received ethics approval to do so in previous studies, including UPSTREAM - Phase I.

We will investigate the baseline characteristics of men who were followed at five years post-randomisation to see how they differ from those who were not followed up.

6.6.2. Measurement bias

Validated questionnaires for PROMs will be used to minimise measurement bias.

6.6.3. Other sources of bias (detection bias)

Given the nature of UDS testing and knowledge of results unpinning treatment decisions, group allocation was not concealed from men (or their clinical care team) during the UPSTREAM trial (Phase I). Where feasible, research staff were blinded to allocation while conducting data collection for outcomes, performing data entry and analysis, and by using Study Numbers only to identify men, questionnaires and other documentation.

All analyses will be clearly predefined in the UPSTREAM - Phase II SAP to avoid bias.

6.7.Withdrawal criteria

Participants will remain in the further follow up study (Phase II) unless they choose to withdraw, or if they are unable to continue for a clinical reason, as notified by the participant or doctor. If a participant withdraws consent, data collected up to the point of withdrawal will be retained (confidentially) for analysis unless the participant specifically requests otherwise, as stated in the PIS. We would continue to collect data from their medical/ electronic (health care) records unless they request otherwise. A study 'Change of Permissions/ Withdrawal' form will be completed in all cases, and databases updated accordingly.

6.7.1. Withdrawal reporting procedures

Study specific procedures for a participant's change of permissions, or withdrawal, will be outlined in the relevant trial working guidelines, which appropriate members of the research team will be made aware of. The PIS will include information for participants.

6.7.2. Post study care

Post study care does not apply to this second phase of the UPSTREAM project (UPSTREAM - Phase II).

6.8 End of Study

The start date for this second phase of UPSTREAM (UPSTREAM - Phase II) is 01 July 2019, and the study duration is expected to be 36 months, to 30 June 2022.

7. Adverse Events

Adverse events (AEs) are typically defined as *"any unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment/ procedures required by the protocol"*. For the purpose of this (low risk) further follow up study, where trial conditions no longer apply, we do not expect, nor will actively seek, any serious adverse events (SAEs) related to research procedures, such as completing a participant questionnaire. If, however, we become aware of relevant information about a participant, we will ensure that it is recorded. In those situations, we would liaise with the Sponsor within a timely manner, noting their relevant safety reporting standard operating procedures (SOPs) and supporting documents.

8. Statistics and Data Analysis

8.1.Planned (recruitment and) five year follow up rates

Between October 2014 and December 2016, 820 men were randomised (enrolled) to the UPSTREAM trial (UPSTREAM - Phase I).[5] For the purpose of this further follow up at five years post-randomisation, Table 2 (below) presents estimated questionnaire follow up targets, taking into account expressed consent to be contacted about long term follow up, and known 18-month (final) follow ups during UPSTREAM - Phase I.

Table 2 **Estimated questionnaire follow up targets for UPSTREAM - Phase II**

			Five years post-randomisation further follow ups	
Calendar Year	**Calendar Month**	**UPSTREAM Project Month #**	**Estimated monthly questionnaire follow up targets[a]**	**Estimated cumulative questionnaire follow up targets**
2019	Oct	67	3	3
2019	Nov	68	1	4
2019	Dec	69	4	8
2020	Jan	70	10	18
2020	Feb	71	8	26
2020	Mar	72	23	49
2020	Apr	73	23	72
2020	May	74	29	101
2020	Jun	75	30	131
2020	Jul	76	28	159
2020	Aug	77	19	178
2020	Sep	78	17	195
2020	Oct	79	27	222
2020	Nov	80	34	256
2020	Dec	81	24	280
2021	Jan	82	44	324
2021	Feb	83	50	374
2021	Mar	84	30	404
2021	Apr	85	39	443
2021	May	86	25	468
2021	Jun	87	36	504
2021	Jul	88	17	521
2021	Aug	89	13	534
2021	Sep	90	12	546
2021	Oct	91	19	565
2021	Nov	92	18	583
2021	Dec	93	17	600

[a] This column is the specific number of men recruited over time for the duration of the recruitment window of the main study (October 2014 to December 2016), revised to take into account expressed consent for patients willing to have longer-term follow up, and known 18-month follow ups of the main trial (UPSTREAM - Phase I) (estimates correct at August 2018).

8.2.Statistical Analysis

Analyses will be conducted by "intention-to-treat" (retaining the original randomised allocation) to assess the broader policy implications of urodynamic testing and/or by a "treatment received" approach to assess the direct impacts of different therapies on men.

8.2.1. Summary of data and flow of participants

Figure 1 and Table 1 illustrate the flow of participants and summarises what data we propose collecting, and when. In brief, eligible men will be asked to complete a one-off questionnaire booklet around five years post-randomisation to the UPSTREAM trial (Phase I). The research team will also request a one-off bespoke data extraction via NHS Digital in 2022 to allow for the last participant's five year follow up timepoint.

Analysis will commence once all five year (questionnaire) follow ups have been completed (or an accepted outcome of invitation is reported).

8.2.2. Outcome analysis

Akin to the analysis at 18-months (UPSTREAM - Phase I), the mean IPSS score in each group will be compared using linear regression. Differences and confidence intervals will be presented, assessing whether they lie below the non-inferiority margin of 1 point. We will adjust for centre and baseline IPSS score.

Surgery rates will be compared using logistic regression, adjusting for centre. All other PROMs will be compared using linear and logistic regression, adjusting for centre and the relevant baseline measure.

During the analysis of the main trial (UPSTREAM - Phase I) it became clear that as well as looking at the surgery rates in the two arms it would be prudent to assess the effectiveness of surgery. Therefore, assessing whether the inclusion of UDS as a decision-making tool leads to surgery that is more/less successful in reducing IPSS scores. We plan to continue investigating this as part of the five year follow up study.

8.2.3. Planned further exploratory analyses

Full details of all analyses will be included in the SAP for this further follow up study (UPSTREAM - Phase II: SAP).

8.2.4. Subgroup analyses

We plan to carry out the same subgroup analyses as those conducted at 18-months (UPSTREAM - Phase I). Full details will be included in the SAP.

8.2.5. Procedures to account for missing or spurious data

All analyses will be based on complete case data and those who are analysable at five-years. We will explore the baseline characteristics of men who are followed up at five-years with those that are not. If appropriate, given the missingness mechanism, we would like to employ imputation methods (such as imputation using chained equations) to impute five-year follow up values for those who we were unable to contact.

8.3.Economic evaluation

An economic evaluation from an NHS secondary care perspective with a five-year time horizon will be conducted. NHS digital will provide information on resource use in terms of participants' inpatient admissions; outpatient attendances; outpatient procedures; radiology; and A&E episodes. Use will be made of the most up to date NHS reference cost grouper application in order to derive Health Resource Groups (HRGs). Department of Health reference costs will be used to value these data.

Differences in costs and QALYs between the arms will be evaluated using appropriate regression techniques adjusting for centre and baseline IPSS, and additionally baseline utility in respect to QALYs.

The outputs from the regressions will be used to estimate Incremental Net Monetary Benefit (INMB) at a range of willingness to pay for a QALY thresholds and if appropriate the Incremental Cost Effectiveness Ratio (ICER).

Uncertainty for all these analyses will be addressed using cost-effectiveness acceptability curves and sensitivity analyses.

9. Data Management and Security (Handling)

9.1.Source data and documentation

Source data is the first place the data is recorded; where data are recorded first in the patient's medical records that is the primary source data. Source data for this study will consist of participant completed questionnaires (paper/online/transcribed to paper via telephone conversation) (questionnaire component of the study), and hospital medical records (NHS Digital data extraction component of the study).

Participants will continue to utilise the same unique participant identification number allocated in Phase I of the UPSTREAM project.

To prevent unauthorised access, personal data entered directly into the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to delegated members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the European Economic Area (EEA) will be anonymised and must abide by a data sharing policy consistent with University of Bristol policy as outlined in Section 13.11.

Data obtained by paper will also be entered onto the password protected database. Information capable of identifying individuals will be held in the database with passwords restricted to UPSTREAM study staff. Information capable of identifying participants will not be removed from University of Bristol or made available in any form to those outside the study, except for NHS digital for the purpose of secure data linkage. All data recorded on paper will be stored in a locked filing cabinet. Participant details will be anonymised in any publications that result from the study.

9.2.Data collection

Details of the components and timing of follow up measures can be found in Table 1 and Section 6.5.

Questionnaires: The research team will send participants a paper copy of the questionnaire around five years post-randomisation, which can be returned via the pre-paid (freepost) envelope provided. Alternatively, men can request to complete the questionnaire electronically (online) or verbally (telephone) with a trained member of the research team.

The BRTC and research team will set up an administrative database system to prompt when patient invitation packs (including questionnaire) need to be sent, are due, and (if applicable) overdue. The research team will monitor questionnaire return. If a participant fails to return a questionnaire, a total of three contacts will be made (as described in Section 6).

NHS Digital: We will also collect some clinical and resource use data via a one-off bespoke extraction of HES and HES-ONS linked data (via NHS Digital). NHS Digital handles information from healthcare organisations in England and Wales, including dates and details for hospital admission/attendance and where applicable, cause of death. To access this information, we will securely share some identifiable information with NHS Digital, such as study (participant) identification number, NHS number, date of birth and gender. All information will be kept secure and confidential. The BRTC and members of the research team have experience of using such methods. We will follow up to date guidance and requirements for the process, when the time comes (expected in 2022).

The UPSTREAM research team will retain all participant data.

9.3.Data handling and record keeping

Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centre (as relevant). All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR); this process will be reviewed and updated accordingly with any updates to the guidelines.

For this study, research data will be kept for *at least* five years after the end of the study, in line with Sponsor requirements. Data from the first phase of the UPSTREAM project (main trial, Phase I) is being kept until 30 September 2028 when plans to destroy will be reviewed. Therefore, we propose that research data from this second, extended phase (UPSTREAM - Phase II) are also held until the same time.

Personal data (e.g. name and address, or any data from which a participant might be identified) will not be kept for longer than is required for the purpose for which it has been acquired.

9.4.Database platforms

All data will be entered and stored onto updated versions of the existing UPSTREAM databases. In order to access the databases, users will be added to the system (following request from the Trial Manager) by the Data Manager. It is the Trial Manager's responsibility to add the user to a specific project and role. Personal details and administration data will be entered on a secure database held on a University of Bristol server, and non-identifiable data (such as questionnaire responses) will be entered onto REDCap. REDCap (Research Electronic Data Capture) is a secure, web-based electronic data capture system designed for the collection of research data. The system has been developed and supported by Vanderbilt University, TN, USA. The BRTC at the University of Bristol has set up its own infrastructure so that all systems are hosted at, and supported by, the University of Bristol.

9.4.1. Administrative Data

The administrative data will be kept in a secure database that is only accessible from within the University of Bristol firewall. All users will require (at least honorary) contracts with University of Bristol in order to access it.

9.4.2. Clinical Data

Data entry can be performed by accessing the REDCap application directly (e.g. by members of the research team) or via the survey function (e.g. if a participant wants to complete the questionnaire online). The clinical data will be stored on a separate server to the administrative data. Anonymised clinical data is linked by a study (participant) identification number. Email addresses are collected as they are essential for the correct functioning of the survey feature. The 'Email Address' field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudo-anonymised at export and does not need further processing. All users will require (at least honorary) contracts with University of Bristol in order to access it.

9.4.3. Storage

North Bristol NHS Trust and the BRTC (University of Bristol) are joint data controllers for the UPSTREAM study. Data will be held at the University of Bristol and will conform to the University of Bristol Data Security Policy and in Compliance with the GDPR as it applies in the UK, tailored by the Data Protection Act 2018.

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

9.5.Access to Data

For monitoring purposes, the Chief Investigator (CI) will allow monitors from the Sponsor (or delegate), persons responsible for the audit, representatives of the Research Ethics Committee (REC) and other Regulatory Authorities to have direct access to source data/documents.

The Data Manager (in collaboration with the CI) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses, see also Section 13.11, below.

9.6.Archiving

An archiving plan will be developed for all study materials. Data will be held in compliance with the Sponsor's standard procedures. Study documents (paper and electronic) will be retained in a secure location at the University of Bristol during the conduct of the trial and for *at least* five years after the end of the study, when all paper records will be destroyed by confidential means. The approval of North Bristol NHS Trust as owner of the data and study sponsor, as well as the CI, will be sought prior the destruction of the data. Where electronic records are in use, the Sponsor's policy will be followed, in agreement with the BRTC.

NB: the current date of archiving end for UPSTREAM - Phase I is 30 September 2028. As stated in Section 9.3 we propose retaining data from UPSTREAM - Phase II until the same time.

10. Project Timetable and Milestones

The start date for this second phase of UPSTREAM (UPSTREAM - Phase II) is 01 July 2019, and the study duration is expected to be 36 months, to 30th June 2022; this period represents months 64 – 99 (inclusive) of the overall UPSTREAM project. Appendix 1 depicts the UPSTREAM - Phase II study Gantt chart.

Milestones include:

- **Months 61-66[a], April – September 2019 (pre-start and early stages):** documentation preparation, research ethics and Health Research Authority (HRA) approvals, set up office including trial management and database systems, and assemble team.
- **Months 67-93 (October 2019 – December 2021):** identify potential participants and conduct five year follow ups.
- **Months 94-98 (January – May 2022):** undertake one-off bespoke data extraction via NHS Digital[b], and undertake analysis of all data.
- **Months 98-99 (May – June):** draft final report (due to funder July 2022).
- **Month 100 plus (July 2022 plus):** dissemination of outcomes and study close down procedures (e.g. archiving).
    - ***HTA Final Report***
    - ***REC study end notification due*** *within 3-months of trial end.*
    - ***REC summary of results due*** *within 12-months of trial end.*
    - ***Others (to be confirmed)***

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[a] these months refer to the overall month of the UPSTREAM project.

[b] We envisage a one-off data extraction of HES and HES-ONS linked data (NHS Digital) will take place in early 2022 to include the last participant's five year post-randomisation timepoint. The exact date of extraction, however, will be decided in collaboration with NHS Digital to maximise data collection within the available grant timeframe. We may conduct an earlier extraction to inform the data analysis; this will be decided as the trial progresses.

11. Trial Management

11.1. Study co-ordination (BRTC)

The trial is supported by the BRTC, UKCRC registered clinical trials unit which, as part of the BTC, is in receipt of National Institute for Health Research CTU support funding. The trial will conform to the BTC SOPs. The research team will prepare all the trial documentation and data collection forms, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

11.2. Chief Investigator (CI)

The CI will take overall responsibility for this study to ensure it is delivered and conducted as required. The CI will be supported by the BRTC, study-specific Trial Manager and other management groups/ committees, as highlighted below. The CI will meet with the Trial Manager and leads of study components at least monthly.

11.3. Day to day management

The research team will be based in the BRTC within Population Health Sciences at the University of Bristol and will provide day to day support for the study. The Trial Manager based at the BRTC will take responsibility for the day to day supervision of study activities. The Study Administrator will provide clerical support to the trial, including organising all aspects of the follow up (e.g. patient packs, including questionnaires: mailing, tracking, and entering returned data). As per BRTC's business and costing model, the Senior IT manager will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the Trial Manager and advice to the team on generic coordination issues. The BRTC Quality Assurance Manager (or equivalent personnel) will oversee and demonstrate that BTC's SOPs for trials have been followed and properly documented, including observance of GCP throughout.

The UPSTREAM research team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting, within increased frequency if needed (e.g. during start-up).

11.4. Project management group (PMG)

The study will be supervised by a PMG. The chair of this group will be Mr Marcus Drake (CI) and will consist of grant holders, representatives from the Study Office and a representative from the Patient Panel; we anticipate this will be the same members as Phase I of the UPSTREAM project. The PMG will meet monthly approximately every 6/7 months throughout the study, or sooner if required. In addition, the PMG will also be invited to meet at the TSC meetings.

11.5. Sponsor

North Bristol NHS Trust, as Sponsor, will be responsible for overall oversight of the study. Delegated responsibilities will be assigned to others taking part in this study.

11.6. Trial Steering Committee (TSC)

The role of the TSC is to monitor and supervise the progress of the study. TSC members from Phase I of the UPSTREAM project have agreed to continue for this further follow up study (Phase II), including the Chairman Prof. Mark Emberton, Professor of Urology at University College London. The TSC will have at least three other independent members, including a statistician, clinician and patient representative, as well as the Trial Manager (Dr Amanda Lewis) and the Chief Investigator (Mr Marcus Drake). Other non-voting members will include the grant holders. Observers may also attend, as may other members of the PMG or members of other professional bodies at the invitation of the Chair.

Given the low-risk nature of this further follow up, we propose that the TSC meet three times throughout the study duration (beginning, middle and end). Additional correspondence will be made if necessary. Existing Terms of Reference will be updated for this phase of project.

11.7. Data Monitoring Committee (DMC)

Given the low-risk nature of this further follow up study, we do not foresee the need for an independent Data Monitoring Committee (DMC), which is supported by our TSC.

11.8. Patient Advisory Group (PAG)

The patient panel (or patient advisory group, PAG) will meet during the early stages of the study (where feasible) to advise on all the trial documentation, including the PIS, questionnaires and recruitment (consent) process. We propose that the PAG meet an additional two times throughout the study to review progress, or more often if needed.

We anticipate using members of our existing patient panel, and/or will source new members as needed. We are committed to obtaining the input of service users at each stage, from design to production of plan English summaries for dissemination. We have patient representation on both our PMG and TSC.

11.9. Funding

This project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 12/140/01).

12. Monitoring, Audit and Inspection

The study will be monitored in accordance with the Sponsor's (North Bristol NHS Trust) Monitoring SOPs, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by North Bristol NHS Trust, REC, the HRA and available for inspection by other licensed bodies.

A trial monitoring plan will be developed by the Sponsor and agreed by the PMG and CI based on the trial risk assessment.

The Sponsor usually delegates some of the monitoring to the research team. The following checks would be typical:

- That consent is received by an appropriately authorised person;
- That written informed consent has been properly documented;
- That data collected are consistent with adherence to the trial protocol;
- That SAE recording, recording of protocol deviations and reporting procedures are being followed correctly;
- That no key data are missing;
- That data is valid; and
- Review of recruitment (follow-up) rates, withdrawals and losses to follow up.

12.1. Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and Sponsor. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, PMG and the TSC (if deemed necessary).

A serious protocol breach will be reported to the Sponsor as soon as possible. The Sponsor will determine the seriousness of the breach and whether onward reporting to the REC is necessary.

12.2. Notification of serious breaches to GCP and/or the protocol and poor-quality data

A "serious breach" is a breach which is likely to affect to a significant degree:

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

The Sponsor must be notified immediately of any case where the above definition applies during the study conduct phase. They will assess the seriousness of any breach as per appropriate Sponsor SOP. Repeated major breaches may be considered serious breaches and notified to the REC and HRA.

13. Ethical and Regulatory Considerations Issues

13.1. Governance and legislation

This trial will be conducted in accordance with:

- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines;
- UK Policy Framework for Health and Social Care Research;
- Data Protection Act 2018; and
- General Data Protection Regulation (GDPR)

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC. The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. If applicable, other specialist review bodies (e.g. CAG) will be notified about substantial amendments in case the amendment affects their opinion of the study.

Before the research team can enroll participants into the further follow up study (UPSTREAM - Phase II), the CI or designee will obtain confirmation of capacity and capability in-line with HRA processes, along with other documentation required for the Sponsor to provide a greenlight letter.

This research trial will be run in accordance with ICH GCP. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

13.2. Peer Review

The proposal for this study has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

13.3. Research Ethics Committee (REC) review and reports

Ethics review of the protocol for the study and other study related participant facing documents will be carried out by a UK REC. HRA approval will be sought alongside REC. Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

ICH GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to ICH GCP guidelines.

13.4. Risks and Benefits

We believe this further follow up study does not pose any specific risks to individual participants, nor does it raise any serious ethical issues.

As with all trials the main benefit of participating is an altruistic one to improve care for subsequent men requiring these interventions. We will also offer men who complete their five year post-randomisation questionnaire a £20.00 gift voucher to reimburse them for their time and any inconvenience throughout the course of the UPSTREAM project.

The PIS will provide clear details of the anticipated risks and benefits of taking part in the study. The risk and benefits of the study will be discussed with the research team (i.e. trial manager and administrator) as part of the process of inviting men to take part.

13.5. Indemnity

This is an NHS-sponsored research study, thus the necessary trial insurance is provided by the Sponsor. North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The PIS provides a statement regarding indemnity for negligent and non-negligent harm.

Specifically, for NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

13.6. Obtaining informed consent from participants

Informed consent will be approached in a proportionate manner according to GCP guidelines. Sections 5 and 6 (Eligibility Criteria and Trial Procedures, respectively) provide details surrounding informed consent for the questionnaire and NHS Digital data extraction components of this further follow up study (UPSTREAM - Phase II).

In brief:

Questionnaire component: Given the 'minor' nature of this questionnaire follow up, we do not propose obtaining additional ('new') written informed consent from men; the burdens are deemed insignificant and sensitive topics are not involved, furthermore, the questions included in the booklet were administered several times to these men during UPSTREAM - Phase I. Instead we will regard the return of the completed questionnaire (paper copy, or completed online or over the telephone), as adequate evidence of consent ("implicit consent"). This approach fits with NHS Research Ethics Committee (REC) guidance (Integrated Research Application System (IRAS) question A30-2 – Recording consent in writing).[9]

Data extraction component: Men who enrolled in the UPSTREAM trial (Phase I) provided written informed consent, which included the essential statement *"I agree that information relevant to the UPSTREAM study may be collected from my hospital and NHS records, including Office of National Statistics (ONS), NHS central*

registers and the Health and Social Care Information Centre, and that this data may be used to follow my ongoing health after the study". Thus, new (additional) consent is not required to request the proposed data via these sources.

13.7. Retention of data

To comply with the 5th Principle of the Data Protection Act 1998 (this process will be reviewed and updated accordingly with any updates to the guidelines), personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the Sponsor's SOPs. Thus, research data will be retained for *at least* five years after close of the study. See Archiving details, Section 9.6.

13.8. Data protection and patient confidentiality

The University of Bristol will be the joint data custodian, with the Sponsor (North Bristol NHS Trust). All data held in Bristol will conform to University of Bristol's Data Security Policy and in Compliance with the Data Protection Act 1998 (or equivalent guidance when applicable).

Questionnaires from participants will be identifiable by participant study number and will be returned by the patient by post (or via electronic/ verbal means) to the UPSTREAM research team. All paper documents will be stored in a secure locked cabinet.

All electronic data files will be saved in a secured computer and to a password protected University of Bristol network space, in accordance with the University of Bristol's data security policies.

Data obtained by paper will also be entered, by trained delegated staff, onto and maintained on an SQL Server database system maintained by UoB Information Services. Information capable of identifying individuals will be held in the database with passwords restricted to UPSTREAM study staff. Information capable of identifying participants will not be removed from UoB or made available in any form to those outside the study.

Data sources will be stored for *at least* five years after the close of the study. Personal data (e.g. name and address, or any data from which a participant might be identified) will be withdrawn from the study if this is requested by a participant.

All nonessential data will be wiped upon completion of the study. Essential documents will be kept for at least five years, after which they will be deleted, and all copies destroyed in accordance with the University of Bristol's secure erasure of data policy.

13.9. Poor quality data

The quality of the trial data will be monitored throughout the trial and data completeness will be reported to the Sponsor and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

13.10. Financial and other competing interests

The research team (including the CI and committee members for the overall trial management), must disclose any ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study. Competing interests will be reported in all publications and in the final report.

13.11. Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the PMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on secure access computers. Requests for access to data must be via a written confidentiality and data sharing agreements (DSA), which will be confirmed by the CI (or appointed nominee); DSA templates are, for example, available from the University of Bristol's research data services facility (RDSF) website.

The DSA should cover limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team. All requests will require their own separate REC approval prior to data being released.

14. Dissemination Policy

Dissemination for the further follow up study will be like that of the trial (UPSTREAM - Phase I), and a comprehensive plan will be developed by the PMG.

To maintain interest in the study, we will send newsletters to participants at suitable intervals. Once results are available, the main forms of dissemination will be through the academic press, HTA monograph, guidelines and workshops for clinical staff and by lay summaries on websites and other more accessible forms for patients. All participants will be offered a lay summary of the main findings of the study (e.g. via newsletters and the study website). Dissemination to clinicians will be through papers in major urology journals and conferences (e.g. the European Association of Urology), workshops and presentations to national meetings e.g. the British Association of Urological Surgeons (BAUS) which is the specialist body with the responsibility for guiding clinical practice, policy matters, research priorities, governance and training in matters related to male lower urinary tract symptoms. BAUS is well placed to implement the findings by informing NHS policy (NICE) and dissemination of evidence-based clinical practice to its members. The Patient Panel working with the trial will assist in the best methods to disseminate the results to patients, including interacting with the relevant charities in this area.

The UPSTREAM trial is part of the portfolio of the new Royal College of Surgeons of England Surgical Centre in Bristol so will be used as a platform for clinical trial training for new surgeon investigators, as well as the opportunity to conduct methodological research in surgical trials which would be disseminated by the surgical centre through workshops and publications.

15. References

1. Jones C, Hill J, Chapple C. Management of lower urinary tract symptoms in men: summary of NICE guidance. *BMJ* 2010; **340**: c2354.
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9. Health Research Authority. Integrated Research Application System (IRAS) Collated Question-specific guidance for NHS REC Form. 2019. https://www.myresearchproject.org.uk/help/hlpcollatedqsg-nhsrec.aspx#1421 (accessed 18 July 2019).
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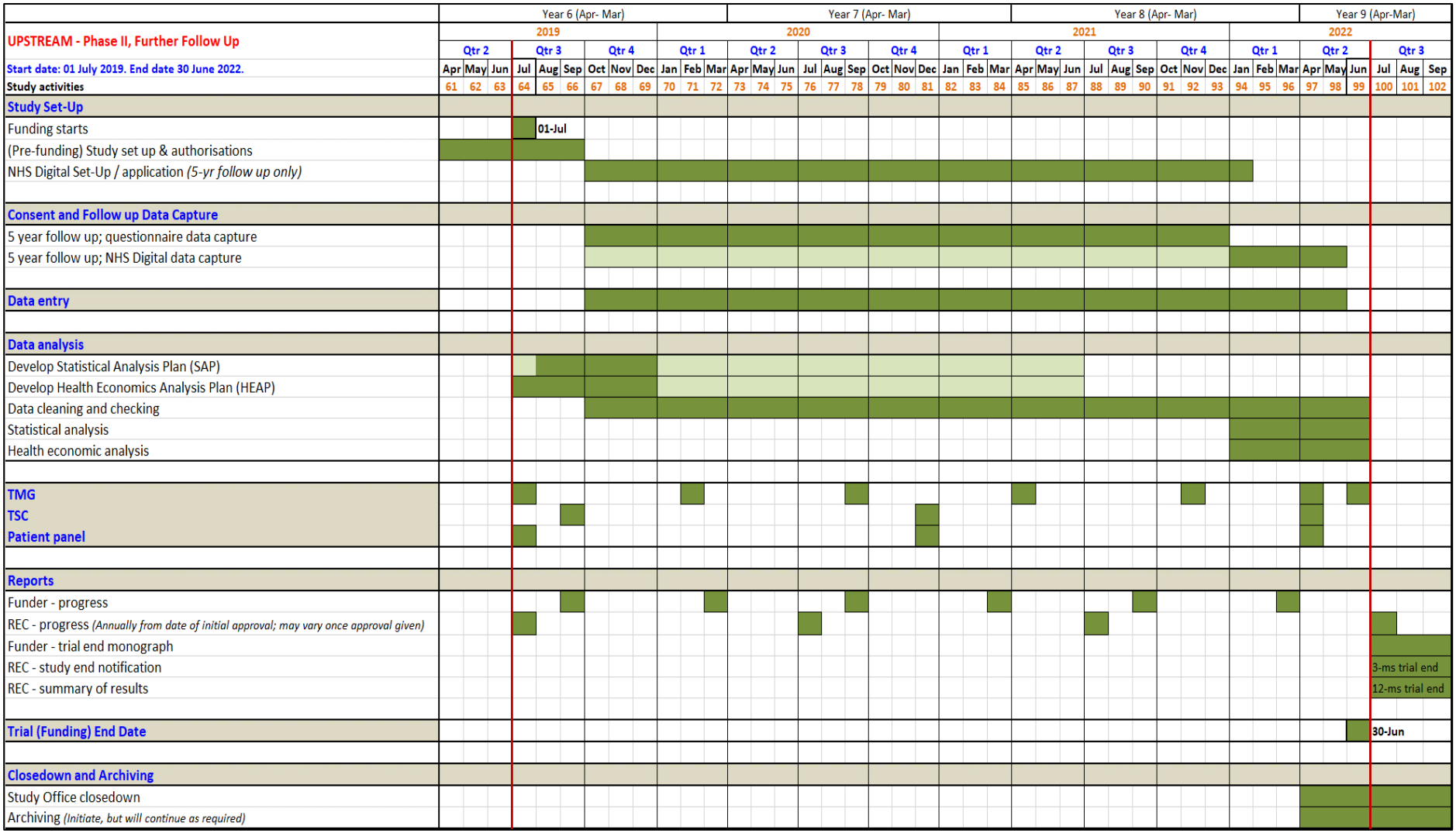
16. Appendix 1. "UPSTREAM – Phase II" Further Follow Up Study Gantt Chart

Start date: 01 July 2019 | Proposed end date 30 June 2022



NB: We envisage a one-off data extraction of HES and HES-ONS linked data (NHS Digital) will take place in early 2022 to include the last participant's five year post-randomisation timepoint. The exact date of extraction, however, will be decided in collaboration with NHS Digital to maximise data collection within the available grant timeframe. We may conduct an earlier extraction to inform the data analysis; this will be decided as the trial progresses.

17. Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended.

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

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the **Study Sponsor**:

Signature: Date (dd/mm/yy):

..../...../.....

Name (please print):

.....

Chief Investigator:

Signature: Date (dd/mm/yy):

..../...../.....

Name (please print):

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Statistician:

Signature: Date (dd/mm/yy):

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Name (please print):

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